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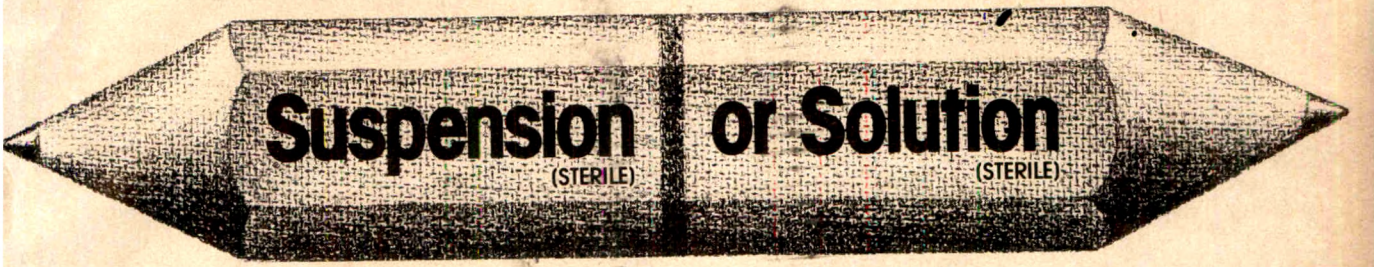
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This drug should be used with care in cases of perforated eardrum and in long-standing cases of chronic otitis media because of the possibility of ototoxicity caused by neomycin.

ADVERSE REACTIONS:
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INDICATIONS:
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Hydrocortisone ..... 10 mg (1%)
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This drug should be used with care when the integrity of the tympanic membrane is in question because of the possibility of ototoxicity caused by neomycin.

ADVERSE REACTIONS:
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When using neomycin-containing products to control secondary infection in the chronic dermatoses, such as otitis externa, it should be borne in mind that the skin in these conditions is more liable than is normal skin to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling, and itching; it may be manifest simply as a failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

PRECAUTIONS:
If sensitization or irritation occurs, medication should be discontinued promptly. Patients who prefer to warm the medication before using should be cautioned against heating the solution above body temperature, in order to avoid loss of potency.

Treatment should not be continued for longer than ten days. Allergic cross-reactions may occur which could prevent the use of any or all of the following antibiotics for the treatment of future infections: kanamycin, paromomycin, streptomycin, and possibly gentamicin.

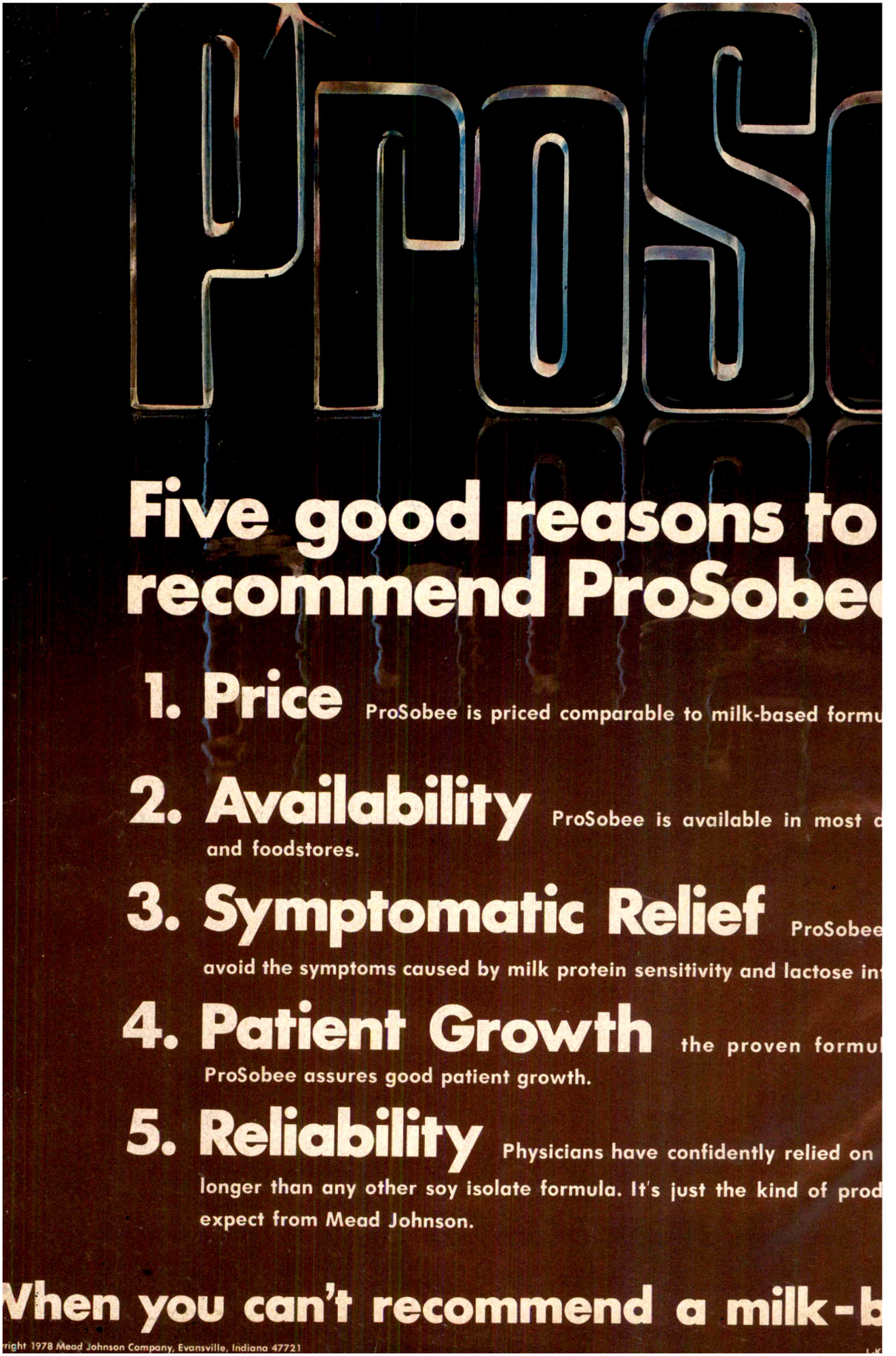
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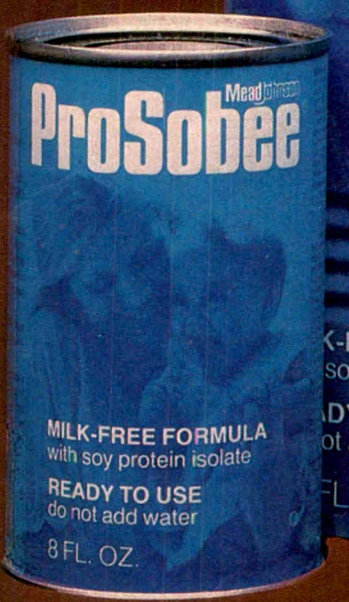
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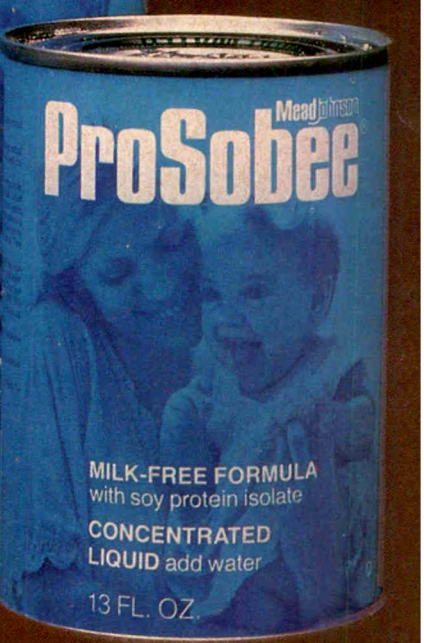

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By using Depakene as part of the initial regimen, you can frequently reduce the need for more toxic agents, and extend your range of therapy from the start of treatment.

Complete prescribing information can be found on the following page along with full disclosure.

1. Sato, S., Dreifuss, F.E., Penry, J.K., Prognostic factors in absence seizures., Neurology, 26:788-796, 1976.
2. Livingston, S., Torres, I., Pauli, L.L., et al, Petit mal epilepsy. Results of a prolonged follow-up study of 117 patients., JAMA, 1974:113-118, 1965.
3. Currier, R.D., Kooi, K.A., Saidman, L.J., Prognosis of "pure" petit mal. A follow-up study., Neurology (Minneap) 13:959-967, 1963.

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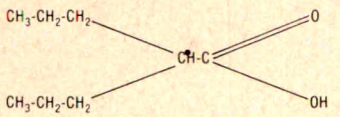
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DESCRIPTION

DEPAKENE (valproic acid) is a carboxylic acid designated as 2-propylpentanoic acid. It is also known as dipropylacetic acid. DEPAKENE has the following structure:



Valproic acid (pKa 4.95) has a molecular weight of 144 and occurs as a colorless liquid with a characteristic odor. It is slightly soluble in water (1.3 mg/ml) and very soluble in organic solvents.

DEPAKENE is supplied as soft elastic capsules and syrup for oral administration.

CLINICAL PHARMACOLOGY

DEPAKENE is an anticonvulsant agent which is chemically unrelated to other drugs used to treat seizure disorders. It has no nitrogen or aromatic moiety characteristic of other anticonvulsant drugs. The mechanism by which DEPAKENE exerts its anticonvulsant effects has not been established. It has been suggested that its activity is related to increased brain levels of gamma-aminobutyric acid (GABA). The effect on the neuronal membrane is unknown.

DEPAKENE is rapidly absorbed after oral administration. Peak serum levels of valproic acid occur approximately one to four hours after a single oral dose of DEPAKENE. The serum half-life ($t_{0.5,8}$) of the parent compound is approximately eight to twelve hours. A slight delay in initial absorption occurs when the drug is administered with meals but this does not affect the total absorption.

A good correlation has not been established between daily dose, serum level and therapeutic effect. Valproic acid is rapidly distributed and the drug is strongly bound (90%) to human plasma proteins.

Elimination of DEPAKENE and its metabolites occurs principally in the urine, with minor amounts in the feces and expired air. Very little unmetabolized parent drug is excreted in the urine. The drug is primarily metabolized in the liver and is excreted as the glucuronide conjugate. Other metabolites in the urine are products of beta and omega oxidation (C-3 and C-5 position). The three major oxidative metabolites are 2-propyl-3-keto-pentanoic acid, 2-propyl-5-hydroxypentanoic acid, and 2-propyl-glutaric acid.

INDICATIONS

DEPAKENE (valproic acid) is indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, including petit mal. DEPAKENE may also be used adjunctively in patients with multiple seizure types which include absence seizures.

In accordance with the International Classification of Seizures, simple absence is defined as very brief clouding of the sensorium or loss of consciousness (lasting usually 2-15 seconds), accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

CONTRAINDICATIONS

DEPAKENE (valproic acid) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

Liver dysfunction including hepatic failure resulting in fatalities has occurred in a few patients receiving DEPAKENE and concomitant anticonvulsant drugs. These incidences have occurred during the first six months of treatment with DEPAKENE. Although a causal relationship has not been established, liver function tests should be performed prior to therapy and every two months thereafter. Caution should be observed when administering DEPAKENE to patients with pre-existing hepatic disease.

Usage in Pregnancy: THE EFFECTS OF DEPAKENE IN HUMAN PREGNANCY ARE UNKNOWN. ANIMAL STUDIES HAVE DEMONSTRATED TERATOGENICITY.

Studies in rats demonstrated placental transfer of the drug. Doses greater than 65 mg/kg/day given to rats, mice and rabbits produced an increased incidence of skeletal abnormalities of the ribs, vertebrae and palate. In rats, there was a dose-related delay in onset of parturition. Postnatal growth and survival of the progeny was unaffected. Embryolethality or major developmental abnormalities occurred in rats and rabbits at doses of 350 mg/kg/day. Studies are being conducted to determine whether there are differences in the toxicity of DEPAKENE (valproic acid) in pregnant rabbits when compared to non-pregnant rabbits.

Recent reports suggest an association between the use of anticonvulsant drugs by women with epilepsy and an elevated incidence of birth defects in children born to these women. Data are more extensive with respect to phenytoin and phenobarbital, but these are also the most commonly prescribed anticonvulsants; less systematic or anecdotal reports suggest a possible similar association with the use of all known anticonvulsant drugs.

The reports suggesting an elevated incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodologic problems in obtaining adequate data on drug teratogenicity in humans; the possibility also exists that other factors, e.g., genetic factors or the epileptic condition itself, may be more important than drug therapy in leading to birth defects.

The great majority of mothers on anticonvulsant medication deliver normal infants. It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of child-bearing potential.

PRECAUTIONS

General: Because of rare reports of platelet aggregation dysfunction, thrombocytopenia and elevated liver enzymes, liver function tests, platelet counts and bleeding time determination are recommended before initiating therapy and at periodic intervals.

Since DEPAKENE (valproic acid) may interact with concurrently administered anticonvulsant drugs, periodic serum level determinations of concomitant anticonvulsant drugs are recommended during the early course of therapy. (See Drug Interactions).

DEPAKENE is partially eliminated in the urine as a ketone containing metabolite which may lead to a false interpretation of the urine ketone test.

Information For Patients: Since DEPAKENE may produce CNS depression, especially when combined with another CNS depressant (e.g., alcohol), patients should be advised not to engage in hazardous occupations, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Drug Interactions: DEPAKENE may potentiate the CNS depressant activity of alcohol.

THERE IS EVIDENCE THAT DEPAKENE MAY CAUSE AN INCREASE IN SERUM PHENOBARBITAL LEVELS, ALTHOUGH THE MECHANISM OF THE INTERACTION IS UNKNOWN. ALL PATIENTS RECEIVING CONCOMITANT BARBITURATE THERAPY SHOULD BE CLOSELY MONITORED FOR NEUROLOGICAL TOXICITY, SERUM BARBITURATE DRUG LEVELS OBTAINED, IF POSSIBLE, AND THE BARBITURATE DOSAGE DECREASED, IF APPROPRIATE.

THERE IS CONFLICTING EVIDENCE REGARDING THE INTERACTION OF DEPAKENE WITH PHENYTOIN. IT IS NOT KNOWN IF THERE IS A CHANGE IN UNBOUND (FREE) PHENYTOIN SERUM CONCENTRATIONS. THE DOSAGE OF PHENYTOIN SHOULD BE ADJUSTED AS REQUIRED BY THE CLINICAL SITUATION.

THE CONCOMITANT USE OF VALPROIC ACID AND CLONAZEPAM MAY PRODUCE ABSENCE STATUS.

Caution is recommended when DEPAKENE (valproic acid) is administered with drugs affecting coagulation, e.g., aspirin and warfarin. (See ADVERSE REACTIONS).

Carcinogenesis, Mutagenesis: There has been insufficient study of the drug in animals to determine whether it has carcinogenic potential. Carcinogenicity studies in rats and mice are currently in progress.

Mutagenesis studies on DEPAKENE have been performed using bacterial and mammalian systems. These studies have provided no evidence of a mutagenic potential for DEPAKENE.

Pregnancy: See WARNINGS.

Nursing Mothers: DEPAKENE is excreted in breast milk. It is not known what effect this would have on a nursing infant. As a general rule, nursing should not be undertaken while a patient is receiving DEPAKENE.

Fertility: Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses greater than 350 mg/kg/day in rats and greater than 90 mg/kg/day in dogs. THE EFFECT OF DEPAKENE (VALPROIC ACID) ON THE DEVELOPMENT OF THE TESTES AND ON SPERM PRODUCTION AND FERTILITY IN HUMANS IS UNKNOWN.

ADVERSE REACTIONS

Since DEPAKENE (valproic acid) has usually been used with other anticonvulsant drugs, it is not possible, in most cases, to determine whether the following adverse reactions can be ascribed to DEPAKENE alone, or the combination of drugs.

Gastrointestinal: The most commonly reported side effects at the initiation of therapy are nausea, vomiting and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps and constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported.

CNS Effects: Sedative effects have been noted in patients receiving valproic acid alone but are found most often in patients receiving combination therapy. Sedation usually disappears upon reduction of other anticonvulsant medication. Ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes", tremor, dysarthria, dizziness, and incoordination have rarely been noted. Rare cases of coma have been noted in patients also on phenobarbital.

Dermatologic: Transient increases in hair loss have been observed. Skin rash and petechiae have rarely been noted.

Psychiatric: Emotional upset, depression, psychosis, aggression, hyperactivity and behavioral deterioration have been reported.

Musculoskeletal: Weakness has been reported.

Hematopoietic: Valproic acid inhibits the secondary phase of platelet aggregation. (See Drug Interactions). This may be reflected in altered bleeding time. Relative lymphocytosis and mild thrombocytopenia have also been noted in isolated cases. Leukopenia has been reported.

Hepatic: Increases in serum alkaline phosphatase and elevations of serum glutamic oxaloacetic transaminase (SGOT) have been noted. Isolated cases of severe hepatotoxicity have been reported. (See WARNINGS).

OVERDOSAGE

A single case of overdosage with valproic acid has been reported. After ingesting 36 grams in combination with phenobarbital and phenytoin, the patient presented in deep coma. An electroencephalogram recorded diffuse slowing, compatible with the state of consciousness. The patient made an uneventful recovery.

Since DEPAKENE is absorbed very rapidly, gastric lavage may be of limited value. General supportive measures should be applied with particular attention being given to the maintenance of adequate urinary output.

DOSAGE AND ADMINISTRATION

DEPAKENE (valproic acid) is administered orally. The recommended initial dose is 15 mg/kg/day increasing at one week intervals by 5 to 10 mg/kg/day, until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 30 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in a divided regimen.

The following table is a guide for the initial daily dose of DEPAKENE (valproic acid) (15 mg/kg/day):

Weight (kg)	Weight (lb)	Total Daily Dose (mg)	Number of Capsules or Teaspoonfuls of Syrup Dose 1	Dose 2	Dose 3
10 — 24.9	22 — 54.9	250	0	0	1
25 — 39.9	55 — 87.9	500	1	0	1
40 — 59.9	88 — 131.9	750	1	1	1
60 — 74.9	132 — 164.9	1,000	1	1	2
75 — 89.9	165 — 197.9	1,250	2	1	2

As the DEPAKENE dosage is titrated upward, blood levels of phenobarbital and/or phenytoin may be affected. (See PRECAUTIONS).

Patients who experience G.I. irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level.

THE CAPSULES SHOULD BE SWALLOWED WITHOUT CHEWING TO AVOID LOCAL IRRITATION OF THE MOUTH AND THROAT.

HOW SUPPLIED

DEPAKENE (valproic acid) is available as orange-colored soft gelatin capsules of 250 mg valproic acid in bottles of 100 capsules (**NDC** 0074-5681-13), and as a red syrup containing the equivalent of 250 mg valproic acid per 5 ml as the sodium salt in bottles of 16 ounces (**NDC** 0074-5682-16).

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Precautions: Hydroxyzine may potentiate the action of central nervous system depressants such as meperidine and barbiturates. In conjunctive use, dosage for these drugs should be reduced. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery.

Adverse Reactions: Drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon dosage reduction. Dryness of the mouth may occur with higher doses. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.

Supply: Tablets, containing 10 mg hydroxyzine hydrochloride, 100's and 500's; Tablets, containing 25 mg or 50 mg, 100's, 500's, and Unit Dose (10 x 10's); Tablets, containing 100 mg, 100's and Unit Dose (10 x 10's); Syrup, containing 10 mg per teaspoonful (5 ml) and ethyl alcohol 0.5% v/v, pint bottles.

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Theophylline relaxes the smooth muscle of the respiratory tract and relieves bronchospasm. Its bronchodilator effect is minimal in the absence of bronchospasm.

INDICATIONS: For the relief of bronchial asthma (acute or chronic) and reversible bronchospasm associated with obstructive pulmonary diseases such as chronic bronchitis and emphysema.

Corticosteroids may be given in conjunction with theophylline, if needed.

CONTRAINDICATIONS: Patients with peptic ulcers, active gastritis, and hypersensitivity or idiosyncrasy to theophylline and other methyl xanthines.

WARNINGS: Should not be given concomitantly with other xanthine-containing drugs or liquids (tea, coffee, etc.) because of the potential for serious toxicity from elevated xanthine serum levels.

Use in Pregnancy: Safety has not been established. Theophylline is excreted in the milk.

PRECAUTIONS: Use with caution in patients with cardiovascular disease, in young children and the elderly, and in patients with liver, kidney and heart disease.

ADVERSE REACTIONS: **Gastrointestinal:** loss of appetite, nausea, vomiting, gastric irritation. CNS: irritability, especially in children, insomnia, headache, dizziness, convulsions. These side effects are usually associated with high theophylline serum levels (exceeding 20 μg/ml.) **Cardiovascular:** palpitations, sinus tachycardia and increased pulse rate, usually mild and transient.

Other side effects may include increased irritation with dehydration, muscle twitching and increased SGOT levels.

DRUG INTERACTIONS: Theophylline increases the excretion of lithium carbonate and may enhance the sensitivity and toxicity of digitalis derivatives and sympathomimetic amines. Doses higher than usual may increase the effect of oral anticoagulants. Concomitant use with erythromycin, clindamycin, lincomycin and troleandomycin may increase theophylline serum levels. Colorimetric methods for serum uric acid are affected by theophylline. Spectrophotometric methods for theophylline in serum are affected by furosemide, sulfathiazole, phenylbutazone, probenecid and theobromine.

DOSAGE AND ADMINISTRATION: Dosage must be individualized. Accepted therapeutic serum levels of theophylline are 10-20 μg/ml. Its metabolism may vary greatly with age, among individuals and in patients with liver, kidney and heart disease. Metabolism may be stable with the same individual. However, careful monitoring for manifestations of toxicity and periodic determinations of theophylline serum levels are necessary, especially for prolonged therapy and when using doses higher than 4 mg/kg/6 hours.

Children: The usual starting dose is 4 mg/kg body weight every 6 hours.

The following table may be used with the Dow graduated measuring spoon:

Body Weight		Dose/6 hours		
lbs.	Kgs.	3 mg/kg	4 mg/kg	5 mg/kg
20	9.0	3 ml	4 ml	5 ml
30	14.0	4 ml	6 ml	7 ml
40	18.0	5 ml	7 ml	9 ml
50	23.0	7 ml	9 ml	12 ml
60	27.0	8 ml	11 ml	14 ml
70	32.0	10 ml	13 ml	16 ml
80	36.0	11 ml	14 ml	18 ml
90	41.0	12 ml	16 ml	20 ml
100	45.0	14 ml	18 ml	20 ml

Monitoring of side effects and serum levels is necessary because of the wide variations of theophylline metabolism in children.

Adults: Recommended starting dose is 100 to 200 mg (2 to 4 teaspoonfuls or 10 to 20 ml) every 6 hours. The adequacy of the dose should be determined by clinical response of periodic monitoring of theophylline serum levels.

May be given after meals with water to minimize possible G.I. irritation.

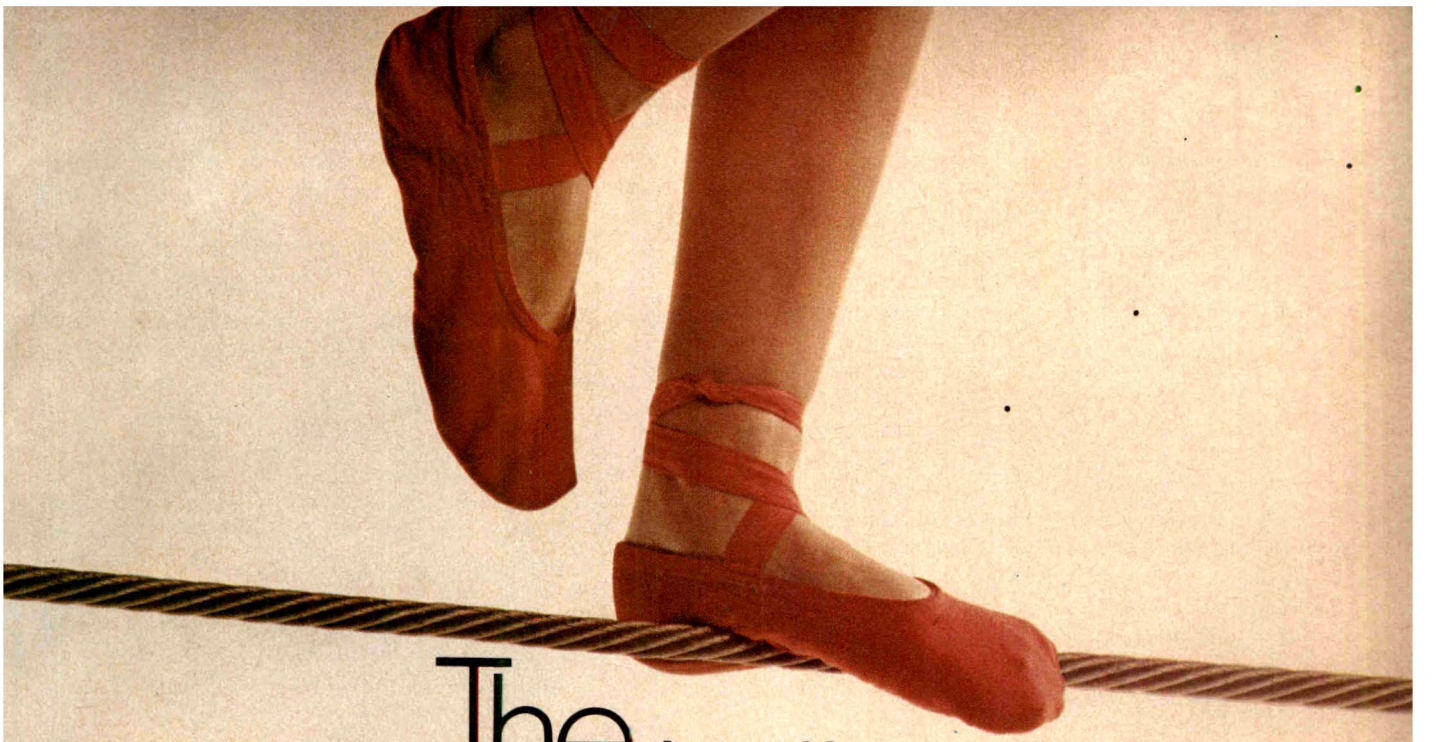
OVERDOSAGE: Theophylline has a narrow therapeutic index and toxicity is likely to occur when serum levels exceed 20 μg/ml. Usual signs of overdosage are anorexia, nausea, vomiting, irritability, headache. Gross overdosage, especially in children, may lead to seizures and death without preceding symptoms of toxicity. Treatment is symptomatic (prompt induction of emesis and gastric lavage, supportive therapy, hemodialysis, etc.).

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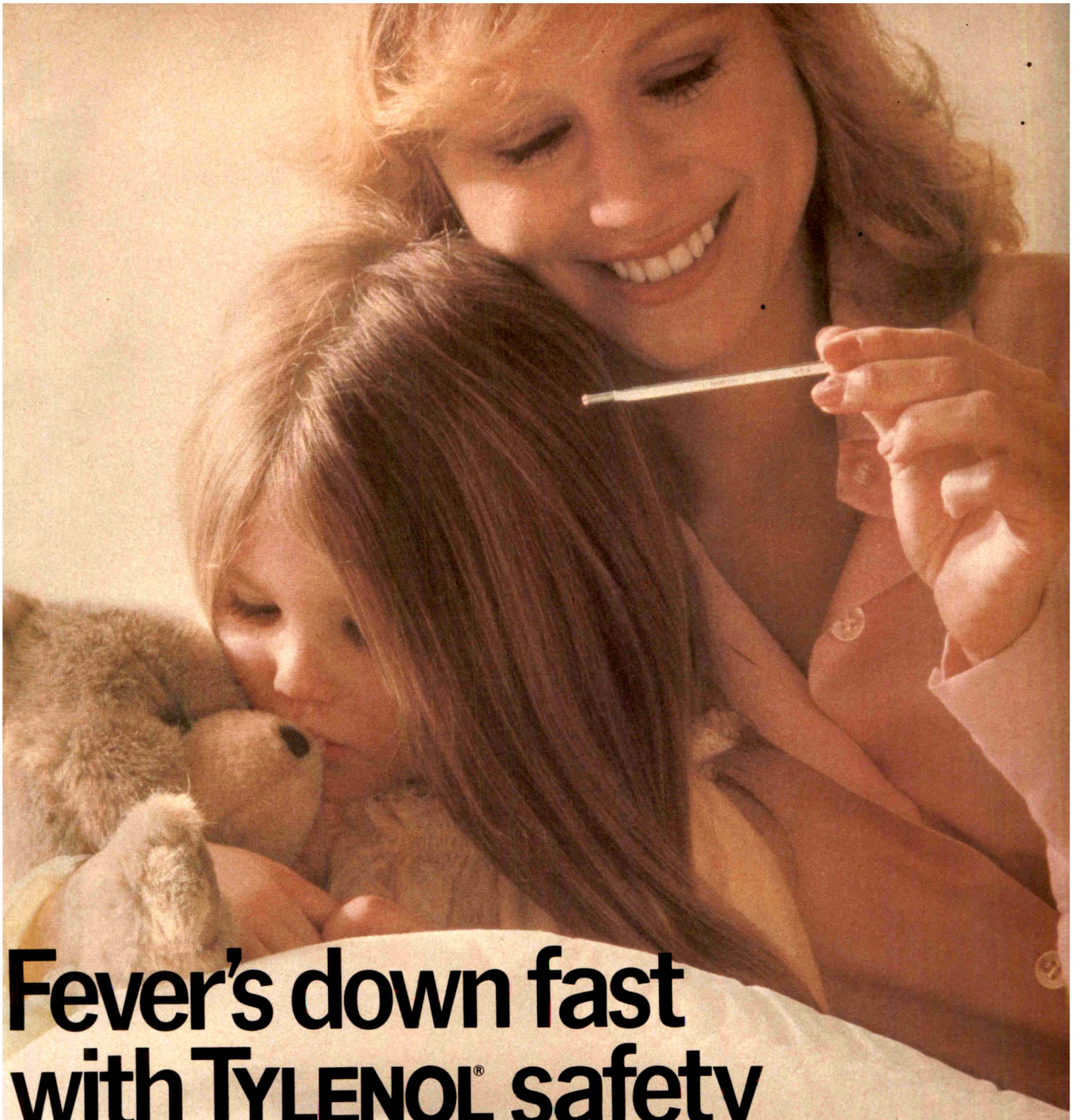
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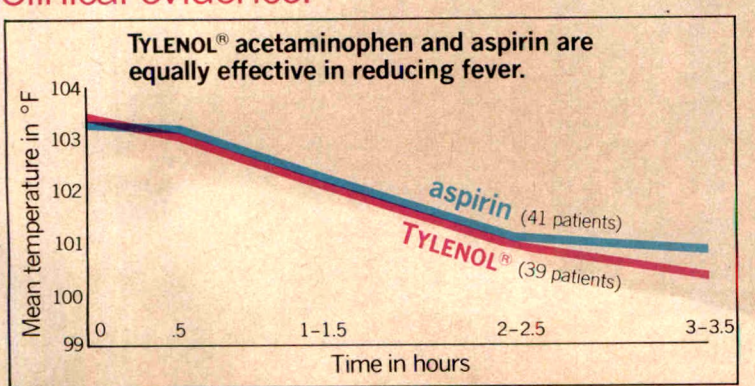
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Dear Reader

Five years have passed since the present editor took up his duties. During this time, I have had the pleasure of corresponding with many authors, some doubtlessly displeased by my negativistic actions, others who were delighted to see their cherished work on the printed pages of the JOURNAL. Both have treated me with courtesy, for which I am truly grateful. The acceptance procedure is a delightful task; the rejection process is not to my liking.

I wish that we could have accommodated more articles; yet, we've not done so badly. These five years have seen the publication of more than a thousand manuscripts, close to 300 BOOK REVIEWS, a host of MARGINAL COMMENTS, together with a string of features—PICTURE OF THE MONTH, RADIOLOGICAL CASE OF THE MONTH, LETTERS FROM ABROAD, LIBRI LIBERIS (a series on children's books), REVIEWS, and RESIDENT SEMINARS. Research articles have been included, even an occasional esoteric one, but in the main, our emphasis has been on the clinical approach. We have captured the George Armstrong Lectures given each year at the Ambulatory Pediatric Association and the Jacobi Award Lectures given at the annual meeting of the American Medical Association. These reflect the current thinking of those who have been recognized for their contributions to pediatrics. The occasional CLASSICS FROM THE MEDICAL LITERATURE are designed to provide an historical perspective and the LETTERS FROM ABROAD, a foreign perspective.

The subject material has ranged over the entire spectrum of pediatrics, from infectious disease (a frequent topic) to genetics, the newborn, the endocrine apparatus, psychosomatic problems, and the learning process, to name but a few. Investigative efforts and clinical observations have both found a place on our pages. Our MARGINAL COMMENTS section is designed to accommodate commentaries on new developments and interpretations, even speculations about things to come. We hope that these have held your interest, and possibly have been of help to you in your work and in your practice.

There is nothing more upsetting to an author than the waiting period between acceptance of his manuscript by the editors and its appearance on the printed page. A certain amount of delay is inevitable: copy editing, layout, author approval, galley-proofing, printing, and mailing processes all take time. But there is an additional reason for delay in publication, which is conveniently known as "backlog." Contracts between publisher and printer call for a specified number of printed pages that cannot be exceeded short of cost overruns. Hence, if too many manuscripts are accepted by the editors, the delays grow longer. For a time, we had a considerable backlog of manuscripts, a situation that we shared with other pediatric journals.

Due to the valiant efforts of the editorial board and the use of a priority system, I can now report to you that our backlog has been reduced to reasonable proportions, to the point where the interval between acceptance of a manuscript and its appearance in print is approximately four to seven months, an interval that most monthly medical publications find very difficult to shorten. Hence, today's message: the editors of the JOURNAL and the publisher's staff will do everything in their power to see that your manuscripts, once accepted, are published as quickly as possible

But papers are written to be read. Dr Samuel Johnson once quipped, "I never desire to converse with a man who has written more than he has read." So what of the reader? The editors in their attempts to bring quality to the JOURNAL want to know what *you*, the reader, think of it. Our LETTERS TO THE EDITOR section is open to all, and the editors welcome your comments and criticisms.

GILBERT B. FORBES, MD
University of Rochester
Medical Center
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Rochester, NY 14642

Seizures, Anticonvulsants, and Pregnancy

The JOURNAL has been the forum for previous comments about anticonvulsant teratogenicity.[1,2] High risks are associated with trimethadione.[3] The risks associated with other anticonvulsants are less and need to be weighed against the hazards of epilepsy during pregnancy. The conclusion that phenytoin induces serious anomalies in 10% of the offspring of epileptics and less major abnormalities in 30%[2] is not supported by the bulk of the literature. The recommendation to discontinue such medication in treated epileptics appears unwarranted.

MALFORMATIONS IN CHILDREN OF EPILEPTICS

Most studies are in agreement that epileptic mothers receiving anticonvulsants are two to three times more likely to have malformed infants than mothers who never had a seizure.[4-13] A number of studies indicate that the incidence of anomalous infants is the same in treated and untreated epileptics.[4-6,14] Others find a greater number of anomalies in treated epileptics compared with untreated patients,[8,12,13] although in two of these studies[12,13] the sample size was probably too small to support such a conclusion. Selection of anomalies in the other report[8] suggested an increased incidence only in the treated epileptics, but reevaluation of the *same data* disclosed *no* difference in *total* or *major* anomalies in treated and untreated epileptics.[6] Minor abnormalities such as distal limb hypoplasia were more frequent in treated epileptics in both studies. A number of frequently cited reports lack the crucial untreated epileptic control group.[7,10,15-17] If differences in rates of anomalies exist between treated and untreated epileptic offspring, they are so small that they would only be recognized in a large series of about 2,000 epileptic pregnant women.[5,14] Several smaller series suggesting teratogenicity acknowledge the inadequacy of data in this regard.[1,8,9,11] Thus, there is no statistical proof of a causal relationship between anticonvulsants and malformations. If such proof is forthcoming, the differences are likely to be small.

The types of serious malformations most commonly seen are cleft lip, cleft palate, and congenital heart disease. Mental deficiency and microcephaly have been observed in offspring of epileptics[7,10,15] and have been attributed to anticonvulsants.[2] These statements about medication effects are based on data that are not controlled for variables discussed elsewhere and lack assessment of parental intelligence and head circumference. Differences noted between children of treated epileptics and those of nonepileptic controls are small. Mean head circumference of children of epileptics was 0.5 cm less at birth and the same at 7 years. Wechsler Intelligence Scale for Children at 7 years was 92 in children of epileptics and 97 in controls.[7] Environmental factors may also play a major role when mothers have a serious chronic illness. These important issues must be assessed before one can accept anticonvulsants as a cause of mental deficiency. It is important to recall that microcephaly is not diagnostic of retardation.[18] This may be particularly true in children with underlying disorders such as congenital heart disease.[19] In general, the CNS is relatively resistant to teratogens.[20] Attempts to define a specific "fetal hydantoin syndrome"[7,15] and phenobarbital syndrome[17] have been done in investigations without an untreated epileptic control group. The specificity of the syndromes is in doubt because they resemble each other and the "fetal alcohol syndrome."

If medication is not teratogenetic as the aforementioned data suggest, why are there increased anomalies in children of epileptic mothers? Genetic factors may play a major role. A greater propensity for dysmorphic abnormalities may exist in these families. However, the sample sizes are generally too small to reach statistical significance, and only trends can be noted. There is a greater prevalence of anomalies in relatives of epileptics.[21,22] Conversely, there is also a high rate of epilepsy in families with cleft lip and palate.[23] The increased incidence of anomalies in offspring of epileptic fathers[6,14] may be further evidence for dysmorphic tendencies in these families. This may be a genetic tendency, as the data in relatives not taking medication suggest, or it may represent a mutagenic effect of drugs before pregnancy. Epileptics themselves have more anomalies than nonepileptics.[6] Seizures may be more common during the first trimester in pregnancies, resulting in a malformed infant,[21,24] but teratogenicity of hypoxia and acidosis remains unproved.

EFFECTS OF EPILEPSY ON PREGNANCY

Epilepsy is the most common preexisting neurological disease encountered by obstetricians[25] and the most common cause of coma during pregnancy.[26] A lack of effect of epilepsy on pregnancy has been summarized mainly in treated patients.[27-29] These series are small, and infrequent complications (less than 10%) could easily be missed. Several larger studies[8,14,25,30] found a greater incidence of obstetric complications in epileptics, including vaginal bleeding and the need for intervention during labor.

Data about fetal-infant morbidity are variable. An increased fetal wastage has been noted by several investigators,[6,8,10] but most observers find no greater rate of stillbirths in epileptics. Neonatal mortality has been reported to be greater in children of epileptics in several studies[5,6,9,30] but not in others.[11,27-29,31,32] The role of seizures themselves in these statistics is not clearly delineated. Burnett[31] reported 20 epileptic gestations with two infant deaths (10%) attributable to seizures. Although normal infants can be born even after prolonged status epilepticus,[33,34] this is commonly disastrous for both mother and child.[11,31,32,34-36] The incidence of status epilepticus varies from 0% to 10% in different series[25,31,32,34] and is probably not increased during pregnancy. A single seizure can result in fetal death.[31] Although medications can sometimes be discontinued during pregnancy,[2] this may cause status epilepticus.[36] It is not surprising that seizures can result in fetal-infant morbidity. The level and duration of hypoxia and acidosis, even in a short seizure, are considerable[37] and similar to that detected with fetal monitoring in asphyxiated newborns with intrapartum anoxia and neurological sequelae.[38]

Many patients in these reports are treated, and presumably the incidence of serious seizures would be higher without anticonvulsant treatment. Thus, the effect of anticonvulsants may bias our assessment of the true hazards of epilepsy during pregnancy. One would hope for the careful documentation of these risks in the preanticonvulsant era. However, such hopes are soon crushed by the realization that careful distinctions between epilepsy and eclampsia were often not made, hysterical seizures were considerably more frequent, and epileptics were discouraged from marriage and pregnancy. The latter was more likely directed to the patient with serious seizures.

EFFECTS OF PREGNANCY ON EPILEPSY

The effects of pregnancy on epilepsy are more clearly documented. Between 30% and 60% of epileptics have more seizures during pregnancy[32,39] perhaps related to lower plasma drug levels.[39] Deterioration of seizure control will usually be evident in the first trimester.[25] Pregnancy is followed by a permanent deterioration in seizure control in 3% of epileptics.[32] Seizure frequency in one pregnancy has little predictive value for seizure frequency in subsequent gestations.

COUNSELING

Many authors recognize the great value of anticonvulsants compared with possible teratogenic risks and recommend continuation of anticonvulsants during pregnancy.* This includes many investigators concerned about possible teratogenetic effects. Epileptics should be counseled about the risk of increased seizures during pregnancy and the small additional risk (less than 10%) of anomalies in comparison with nonepileptics. Many of these, eg, cleft lip and palate, are treatable. The risks are probably less when there is no other family history of anomalies. Only one group[2,7] has proposed guidelines that would actively discourage anticonvulsants during pregnancy. However, their studies lack the appropriate controls discussed previously. In some of the reports of cases already mentioned, biased conclusions may have resulted from uneven selection of rates of patients (Berkson fallacy).[41]

CONCLUSIONS

Infant malformations are a more prevalent outcome in pregnancies in epileptics. Genetic factors may play a major role, and counseling should be based on a careful family history of malformations. Anticonvulsants have no *proved* teratogenicity and *if* they have such an effect, it is small. Seizures during pregnancy sometimes result in infant and maternal morbidity and mortality. Seizure frequency increases in one third to two thirds of epileptics during pregnancy. The rate of other complications is probably between 5% and 10%. Seizures would probably have a much greater adverse effect on pregnancy if anticonvulsants were not in use. General principles of anticonvulsant therapy require that patients be taking the minimum dose and number of medications necessary to control their seizures. Relative risks are such that these medication considerations should not be altered in epileptic patients contemplating pregnancy, with the exception of those taking trimethadione. Drug doses may need to be adjusted during pregnancy to maintain therapeutic levels.

Data on anticonvulsant teratogenicity show the need for control groups; omission of the control groups has produced unwarranted conclusions.

DAVID A. STUMPF, MD, PhD
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Immunity After Rubella and Measles Viral Vaccines

During the early stages of clinical trials with live attenuated rubella vaccines about a decade ago, two important questions were paramount in the minds of those responsible for those trials. The first was concerned with the possible communicability of the vaccine virus and the second with the duration of immunity. It must be accepted that any new vaccine poses problems, both general and specific, but as far as rubella vaccines were concerned, these were of special importance.

The first question arose from the original trials in a small group of susceptible children carried out by Parkman et al[1] and Meyer et al[2] with their high passage virus (HPV-77) prepared in monkey kidney cell cultures. They had shown that intermittent excretion of rubella vaccine virus occurred in the majority of vaccinated individuals. The question was simple. If vaccinees excreted virus in the nasopharynx, could infection be transmitted to susceptible contacts and, more important, if the contact was a pregnant woman, could the vaccine virus cause damage to the fetus?

Fortunately, for one reason or another, possibly due to the fact that the vaccine virus in the nasopharynx was usually excreted in low titer, transmission of infection to susceptible contacts could not be detected.

This fact was fully confirmed by the extensive trials of other live rubella vaccines between 1967 and 1969.[3-5] Nevertheless, at the time it was the most important potential drawback to the licensure of live rubella vaccines which, although attenuated in the sense that they produced very little clinical disease, had the propensity of spreading and could by no yardstick be regarded as attenuated or nonteratogenic for the human fetus that they were designed to protect. All current immunization programs against rubella are based on the fact that the vaccine is safe to administer to children and young adults and that no restrictions need be placed on them for fear of transmitting infection to their mothers or others with whom they might come into contact.

The second question, that of the duration of immunity, was, and still is, a far more difficult one to answer. Many natural infections, including smallpox, yellow fever, poliomyelitis, measles, and rubella, give rise to a life-long immunity in that clinically and virologically proved second attacks are very rare events. It used to be taught that live attenuated vaccines, such as smallpox and yellow fever, were to be preferred to inactivated vaccines because they gave rise to life-long immunity (which they clearly did not). Revaccination against smallpox was a statutory requirement for travellers for many years so that immunity could be maintained. Drawing a distinction between life-long and long-term immunity is not just a matter of semantics, there is an important difference. Only careful and continued surveillance of immunized populations can answer the question as to whether vaccines currently in use against poliomyelitis, measles, and rubella for example, can confer the same effective immunity that follows natural infection.

The present success with measles vaccine in the United States reported by Krugman[6] is encouraging, but it would be foolhardy to assume that success with a measles vaccine is necessarily going to be the same as with a rubella vaccine. First of all, the two viruses are different, the vaccines are different and the two diseases are different. Measles is essentially a disease of early childhood capable of causing severe disease, particularly in the presence of malnutrition, whereas rubella is a disease of older children and adolescents in whom it causes little serious disease unless it occurs in pregnancy. The purpose for which measles and rubella vaccines are administered is therefore all important. Measles vaccine is administered to confer direct protection to the individual; rubella vaccine is administered to confer protection indirectly to an unborn fetus at some later stage in the life of the individual. The two vaccines do not necessarily have to be administered together, though it may be convenient to do so if combined vaccines are available.

The procedure now recommended in the United States is to offer rubella vaccine to all children, both boys and girls from approximately 15 months of age to puberty.[7] This would have the dual objective of conferring immunity on a large proportion of the childhood population before they acquired natural infection and also of suppressing or otherwise controlling the reservoir of infection. In theory, elimination of wild virus from the community by mass vaccination would remove the main source of the cause of congenital rebella defects, but it would also remove the most effective means of maintaining immunity in vaccinated communities. Unless there is a very high acceptance-rate of vaccine, rubella will continue to occur in vaccinated communities. This has already been reported in several areas in the United States with outbreaks of rubella occurring mainly in unvaccinated susceptible individuals.[8] In Britain and many European countries, selective immunization is used for schoolgirls aged 11 to 14 years, leaving boys unvaccinated. Most countries now recommend immunization of adolescent girls and women if serological tests indicate that they are susceptible. This then is the essential difference between the so-called American and British schemes to control congenital rubella defects—for this after all is what rubella immunization is all about.

The crucial question to be answered with respect to rubella is whether vaccine-induced immunity is as effective and durable as immunity from the natural disease. On this depends the whole question of the age at which the vaccine is best administered. As for natural immunity, there is good evidence that primary infection in childhood leads to immunity lasting for many years but it is not known with certainty how immunity is maintained. It could be that humoral immunity persists for prolonged periods after the primary stimulus to the immune mechanism, or that periodic reinfection occurs producing a booster or reinforcing effect to immunity. In this situation, one would expect the secondary type response to be associated with the rapid appearance of antibody of the IgG type. Horstmann and her colleagues[9] have shown that reinfection occurs much more frequently after vaccination than after natural infection. In one study in military recruits,[9] the reinfection rate after administration of Cendehill vaccine was 80% compared with 3.9% in naturally immune individuals. Reinfection was entirely asymptomatic and it is generally assumed that viremia does not occur in a reinfection.

Several reports have recently appeared that indicate that immunity after vaccination may not be as long-lasting as originally anticipated. Dr Dorothy Horstmann carried out a surveillance of rubella vaccines on several hundred children immunized in 1968, with the HPV-77 duck embryo vaccine (HPV-77 DE5).[10] Several important points emerged from the study. First, the number of children with low antibody titers (1:8 to 1:16) was higher in the vaccinated group (30%) than in those naturally immune and a further 60% of the vaccinated group had hemagglutination inhibition antibody levels in the median range. Second, there was a noticeable difference in the number of children who had lost antibody after vaccination when tested three to five years later. Of the vaccinated group, 23% had no detectable antibody and this was mainly in the group that showed a poor initial response. Of these, asymptomatic reinfection developed in 12%,

whereas none of those who were naturally immune or who had high initial titers did so.

In the original trial, it seemed that there was rather a large number of "vaccine-failures"; 118 children were so classified because there was no detectable antibody two months postvaccination. However, it is now well known that if the first postvaccination sample is collected too early, that is to say six to eight weeks after vaccination, then the percentage of seroconverters will be lower than when the second sample is collected eight to 12 weeks after vaccination. The percentage of seroconverters will then be in the region of 95% to 98%. Of the children designated as vaccine-failures, and retested,[10] 82% were found to have detectable antibody three years after, and from the type of antibody response, it looked as if these had in fact responded to the administration of the vaccine rather than a naturally acquired immune response having developed.

A later report published in a recent issue of the JOURNAL (132:573-577, 1978) by Doctors Balfour and Amren from the University of Minnesota, Minneapolis, has shown a substantially high serological failure rate in children given rubella, measles, and mumps vaccines, either as a monovalent vaccine or in a combined form. It is difficult to be certain that these were true vaccine-failures or nonseroconverters since antibody tests were not carried out after vaccination in as much as this was part of a routine primary health care program. It is possible that some children labelled as vaccine-failures had lost antibody, possibly in cases, as Horstmann found, where the initial antibody response was low. On the other hand, the number of seronegative children was higher in those groups immunized between 11 and 13 months than in the 14- to 16-month group, suggesting that residual amounts of maternal antibody could have the same suppressive effect as occurs when measles vaccine is administered at too early an age.[6]

Altogether, 58 of 159 children (36%) had no detectable rubella hemagglutination inhibition antibody at a mean age of 4.7 years postvaccination. With measles vaccine, the same pattern was observed; the overall serological failure rate was 18% (31/168 children) and here again, the age of immunization seemed to be a determining factor in achieving a satisfactory seroconversion rate. The failure-rate with mumps vaccine was only 9%. It could be that some of these children had very low levels of rubella antibody undetectable by standard tests and who were in fact immune. Krugman[8] found this to be the case in a study of a number of children in whom measles antibody had declined after a period of 11 years. When given a second inoculation 14 years later, a typical booster response with rapid appearance of antibody developed.

Balfour and Amren have considered various possibilities to explain these unusual events. Loss of potency in the vaccine is one possibility, but several batches of vaccine were used over a period of time. Although this cannot be ruled out, it is well known that measles and rubella vaccines are labile products sensitive to heat and light and unless meticulous attention is paid to the details of storage, particularly when reconstituted, potency can be rapidly lost. This might occur more frequently when large numbers of children are being immunized in clinics as opposed to the somewhat different setting of a clinical trial.

In a sense, these findings are not dissimilar from those of Horstmann[10] from which two supplementary questions arise. If such a high proportion of children are found to be seronegative four to five years after rubella vaccination, whatever the cause, what will be the position 20 to 25 years later when these vaccinated children will have reached the age of child-bearing? Will they continue to respond to reinfection with an asymptomatic, nonviremic illness? After passage of time, will the effect of the primary antigenic stimulus cease to be effective, in which case could reinfection be associated with symptomatic disease, viremia, and a risk to the fetus? One way to answer this question is to revaccinate a group of these seronegative children to determine the type of immune response. This would seem more reasonable than to challenge them with wild virus to try and determine the presence or absence of viremia which would be an extremely difficult procedure to evaluate.

These are questions that require urgent answers and until they are evaluated, the question of reimmunization of children vaccinated in early childhood will have to be kept open. In any case, there does seem to be an important message of practical importance that reinforces the recommendation of the American Academy of Pediatrics that measles and rubella vaccines should not be given before the age of 15 months (except in the case of measles vaccine where indicated in the first year of life). But are 15 months and early childhood still too early for rubella vaccination, bearing in mind that the threat to be averted lies many years in the future?

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Skeletal Trauma in Skateboard Injuries

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• Thirty fractures resulting from skateboarding have been treated in the past six months at the Henry Ford Hospital, Detroit. Although there have been no serious or unusual injuries, this represents a substantial increase over the previous year. Awareness of the hazards of this sport is the first step in reducing the frequency and seriousness of these injuries. As a result of our experience, safety guidelines for skateboarding are recommended for the parents of enthusiasts. We hope adherence to these guidelines will greatly reduce the number of injuries.

(*Am J Dis Child* 132:751-752, 1978)

There are now an estimated 20 million skateboard enthusiasts in the United States. This renewed interest in the sport of skateboarding resulted from the introduction of urethane wheels, which permit better control of the skateboard. The increased popularity of the sport has lead not only to a monthly magazine, *Skateboarder*, but also to the formation of organizations such as the International Skateboard Association, the Professional Skateboard Association, and the American Skateboard Association.

Although the skateboard was once considered a toy, national championships are now televised by major sports networks. Skateboarders are no longer satisfied with driveways and sidewalks. They are now maneuvering about in swimming pools and schussing down parking structures and abandoned highways. There are approximately 175 skateparks, with another 200 to be built in the near future. Along with this growing interest in skateboarding,[1-3] there has also been an increase in the number of skateboard injuries. According to one observer, "In no other individual recreational sport has one seen such a high morbidity as [in] skateboarding!"[1]

Parents and enthusiasts rarely consider the possibility of serious injury or death from a skateboarding accident. Deaths have resulted from collisions with automobiles[2] or simple inadvertent falls. Injuries that require splenectomies[1] and nephrectomies[4] are further indications of the serious risks and hazards of skateboarding.

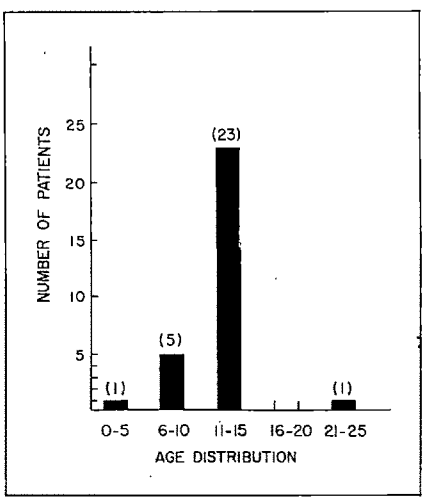
Unfortunately, only limited information concerning skateboard injuries has been published. According to the Federal Consumer Products Safety Commission, the total number of estimated skateboard injuries in 1976 increased to 188,000. This represents a 160% increase from the 82,000 injuries reported in 1975. The commission also reported 28 deaths since 1975. The purpose of this article is to present our series of skeletal fractures resulting from skateboarding and to recommend measures to prevent them.

PATIENTS

From May 1977 through October 1977, 29 patients were treated for 30 fractures resulting from skateboarding. All patients were seen at the Henry Ford Hospital, Detroit, or at one of the two satellite centers. The initial treatment was in the emergency room, except for two patients who attended the orthopedic clinic for follow-up care. Follow-up ranged from two to seven months because of the recent time span. There were 20 males and nine female patients. The ages ranged from 2 to 24 years, and the distribution is shown in the Figure. The average age was 13.5 years. A refracture of the distal radius during another skateboard accident accounted for two fractures in one patient. Two of the patients were brothers.

RESULTS

Of the 21 upper extremity fractures, there were two fractures of the clavicle, three of both bones of the forearm, 15 of the distal radius, and one of the navicular bone. Of the nine lower extremity fractures, there was one fracture of the femur, one of the tibia, five of the ankle, and two of the metatarsus. The fractures in the upper extremity showed no predilection for the dominant hand. There were no compound fractures and no patient required surgery. Four of the 29 patients were hospitalized as part



Age distribution for 29 patients treated for fractures resulting from skateboarding.

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of their initial treatment. All of these patients sustained trauma to the lower extremity. A 3-year-old boy fractured his femur while attempting to step onto a skateboard. He was hospitalized and placed in 90-90° skeletal traction. Three patients with ankle fractures were admitted to the hospital for observation after closed reduction and casting in the emergency room.

The residual disability from these fractures is difficult to evaluate because of the short period of follow-up. However, from the information available to date, no disability is expected in the future nor were the fractures of the type leading to serious disability. All fractures have healed and the patients with epiphyseal injuries will be followed for possible sequelae. No complications were encountered when the patients were hospitalized or when they were attending the clinic. The one refracture in this series is not considered to be a complication. Two months after his long-arm cast was removed, this patient fell the first time back on his skateboard. He sustained a refracture of his distal radius that had been found to be clinically and roentgenographically healed at his last clinic visit.

COMMENT

Soft tissue trauma such as sprains, abrasions, contusions, and lacerations account for the majority of injuries. Fractures occur in perhaps only 10% of the cases and are found predominantly in the upper extremity. The more serious injuries include concussion, blunt trauma to the abdomen, and injuries to the eyes. Neurologic sequelae of hemiplegia and global aphasia have also been reported.[4]

In the present series, there were no unusual orthopedic injuries as a result of skateboarding. Shattered olecranon processes have been reported[2] and the injury referred to as a "skateboard elbow." We have not found this to be a common injury of skateboarders. No serious ligamentous injuries were seen during this period. The general surgery and neurosurgical departments of our hospital have not encountered the severe injuries reported elsewhere.[1,2]

Although the types of fractures have not been unusual, the sudden increase in incidence is noteworthy. No fractures resulting from skateboarding were treated at Henry Ford Hospital in the one year preceding the study. Thirty fractures, however, were seen and treated in the past six months. With the opening of several skateparks next spring, we expect the skateboarding craze to continue and the number of injuries to parallel this trend, especially with speeds reaching close to 40 mph.

Recommendations

To reduce the number of injuries and the possibility of serious harm, several preventive measures can be recommended to parents and skateboarders. The International Skateboard Association, Costa Mesa, Calif, has published a sheet of safety rules titled "Safety tips to parents on skateboarding." Several authors[4-8] and associations such as the National Safety Council, the National Skateboard Association, and the Consumer Product Safety Commission have also recommended safety guidelines. With our recent experience in treating skateboard injuries, we believe these guidelines are best summarized as follows: (1) the proper equipment must be used at all times. Buy a well-made skateboard with the trucks fastened firmly through the board. The board should be selected to fit the size and age of the rider. (2) Maintain the equipment in proper working order. Examine the skateboard, wheels, and trucks regularly and make adjustments and repairs as necessary. (3) Protective clothing, including helmet, tennis shoes, knee pads, elbow pads, and gloves, should be worn whenever skateboarding, not just at skateparks. The wearing of long pants and long-sleeved shirts will help reduce cuts and abrasions. (4) Become familiar with the route and check it for stones, cracks, or possible obstructions before skateboarding. (5) Talk to police and other authorities concerning local ordinances prohibiting skateboarding. Skating on city streets should be avoided at all costs. (6) Master the basic skills before attempting more difficult maneuvers. (7) Control of the skateboard, rather than speed, should be emphasized. (8) Prohibit children from being towed by bicycles or other vehicles. (9) Children must demonstrate balance and coordination, such as in bicycling, before being allowed to ride a skateboard. (10) Instruction in the proper falling and rolling techniques will help reduce injuries, especially to the outstretched arm. (11) Skate only when in good physical condition and after completing warm-up exercises. Do not skate when fatigued.

Although serious skateboard injuries appear to be infrequent, every measure should be taken to prevent them. Educational programs such as the "Skateboard safety clinic," which is sponsored by the International Skateboard Association, should be encouraged and supported. With the proper equipment, good judgment, and adherence to safety guidelines, skateboarding will become a safe and exciting sport.

Sally Ann Miller, executive director, International Skateboard Association, Costa Mesa, Calif, provided information for this article.

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Newborn Head Size and Neurological Status

Predictors of Growth and Development of Low Birth Weight Infants

P 24,251

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• **One hundred eighteen infants with birth weights of 2,000 g or less were evaluated for growth and development at approximately 5 years of age. Review of neonatal data indicated that head circumference less than the tenth percentile at birth and abnormal neurological examination in the newborn period were important predictors of outcome. Both of these factors were associated with poor growth, later microcephaly, and neurological deficit. In addition, neonatal microcephaly was substantially related to poor intellectual attainment. Other associations were seen between microcephaly at birth and intrauterine growth retardation, low Apgar score, and low socioeconomic status, factors that also correlated with poor outcome.**

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Numerous studies of the intellectual and physical outcome of low birth weight infants have been made over the past 25 years. Considerable variability in results has stemmed from unclear identification of patient population, discrepancies in direction of follow-up, differing testing methods, and, over time, levels of perinatal care. Nevertheless, there is general agreement that certain information from the perinatal period is of value in predicting developmental potential in these infants. For example, very low birth weight,[1] perinatal hypoxia,[2] and poor socioeconomic conditions[3] have each been associated with an increased incidence of neurological or intellectual deficit.

In a survey at age 4 to 5 years of children who were admitted to intensive care nurseries in Syracuse, NY, in 1971, two specific associations between neonatal status and outcome emerged that have not generally been reported. These factors were the presence of small head size at birth and the recognition of abnormal neurological behavior in the newborn period. Their association with later handicap forms the basis of the present report.

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MATERIALS AND METHODS

From Jan 1 to Dec 31, 1971, 177 infants with birth weights between 750 and 2,000 g were admitted to the neonatal intensive care units of the Crouse-Irving Memorial Hospital or the St Joseph's Hospital, Syracuse, NY. Table 1 gives the patient population and the survival and follow-up statistics as a function of birth weight. Overall, 128 of these 177 infants (72%) were discharged from the nursery. Three children died later, leaving 125 long-term survivors. One hundred and eighteen children (57 boys and 61 girls), including two twins of birth weights 2,098 and 2,120 g, were evaluated for growth and development at approximately 5 years of age. Of the four boys and three girls who were lost to follow-up, five had birth weights greater than 1,500 g, but did not differ from the remainder of the study group in any other way.

Eighty-one of these infants were born at the aforementioned hospitals; 37 were transported from a 15-county rural referral area. The characteristics of in-born and transported groups were similar. Although 30 of the 37 transported infants were cared for at St Joseph's Hospital, nursery procedures and staff physicians were the same in the two institutions.

The expected date of confinement was determined by the date of the last menstrual period that correlated with a clinical estimate of gestational age in all but one case. Infants were classified as small for gestational age if their birth weights were less than the tenth percentile for the estimated gestational age. Standard care included maintenance of temperature in the neutral thermal range, infusion of intravenous dextrose in water and electrolytes, and institution of oral feedings as soon as possible using formulas containing 67 to 80 calories per 100 ml. Umbilical arterial catheters were placed in infants who had respiratory distress, and inspired oxygen concentration was regulated to maintain Pao_2 between 60 and 80 mm Hg. Continuous positive airway pressure was used for infants requiring an oxygen concentration greater than 70%, and a volume respirator was used for infants with severe apnea or respiratory failure. Hyperbilirubinemia was treated with phototherapy or exchange transfusion and infection with ampicillin sodium and kanamycin sulfate. Routine ophthalmologic examinations were performed at the time of discharge. Parents were allowed unrestricted visiting and were encouraged to visit their infants as frequently as possible.

Obstetric and neonatal medical records were reviewed and summarized. The occipitofrontal head circumference was recorded as the percentile for estimated gestational age from standard charts.[4] Microcephaly was defined as a measurement less than the tenth percentile. Newborn neurological status was designated as abnormal if one of the following were present: hypotonia, hypertonia, severe lethargy, seizures, or abnormal skull transillumination.

Other chart data collected included complications of pregnancy, size of infant related to gestational age, Apgar score, presence of respiratory distress, apnea and hyperbilirubinemia, and rate of growth. Complications of pregnancy, labor, and delivery included bleeding, rupture of membranes more than 24 hours, eclampsia/preeclampsia, breech presentation, fetal bradycardia (heart rate less than or equal to 100), and meconium staining of amniotic fluid. Education of parents and socioeconomic status based on years of

education and occupation of the head of the household were determined.[5]

The children were evaluated between the ages of 4 years 3 months and 5 years 6 months by examiners who had no knowledge of perinatal histories. An extensive medical and developmental history and physical examination, including neurological assessment were performed. Measurements of weight, standing height, and occipitofrontal head circumference were plotted on standard growth charts.[6,7] Audiologic examinations were performed by one of the authors (C.T.G.). Speech was assessed by the Denver Articulation Screening Examination, and if abnormal, was further evaluated by a speech pathologist. Visual acuity and muscle balance were also tested. The Goodenough-Harris drawing test was administered to all children and scored on the basis of 73 characteristics[8] by two independent observers. No correction for prematurity was made for analysis of growth or intelligence quotient. Significance of differences was evaluated using χ^2 analysis, Fisher exact test, or Student's t test when appropriate. A P value of less than .05 was considered statistically significant.

RESULTS

Nineteen of the 106 infants (18%) whose head circumference was measured at birth had measurements less than the tenth percentile; 48 (45%) had measurements between the 10th and 25th percentile, 22 (21%) had measurements between the 26th and 50th percentile; and 17 (16%) had measurements greater than the 50th percentile. Thirteen of 118 infants (11%) had an abnormal neurological examination during the newborn period.

Table 2 relates newborn head circumference and neurological status to other perinatal data and to socioeconomic status. The infants who were microcephalic had a somewhat lower mean birth weight that was secondary to the increased number of small-for-gestational-age infants (53%) in that group. There was an increased incidence of low Apgar score and a decreased incidence of acute respiratory distress in the microcephalic group. No other difference in labor, delivery, or neonatal complications was found to relate to neonatal head circumference. There was, however, a substantial association between small head circumference at birth, low socioeconomic status, less maternal education, and maternal age of 18 years or less.

No substantial differences in any perinatal factors were noted between infants with normal and abnormal

Table 1.—Survival and Follow-up as a Function of Birth Weight

	Birth Weight				
	750-1,000 g	1,001-1,250 g	1,251-1,500 g	1,501-2,000 g	Total
Total liveborn	20	26	31	100	**177**
Nursery survivors	6 (30%)	15 (58%)	24 (77%)	83 (83%)	**128** (72%)
Died after discharge	0	2*	0	1†	**3**
Adequate follow-up	6	12	23	77	**118**
Lost to follow-up	0	1 (6%)	1 (4%)	5 (6%)	**7** (5%)

*Sudden infant death syndrome at age 3 months. Streptococcal meningitis at age 6 months.
†Plugged tracheostomy tube at age 3 months.

Table 2.—Perinatal Data in Relation to Newborn Head Circumference and Neurological Status

	Head Circumference at Birth, Percentile (%)				Neonatal Neurological Examination	
	< 10 (N = 19)	10-25 (N = 48)	26-50 (N = 22)	> 50 (N = 17)	Abnormal (N = 13)	Normal (N = 105)
Birth weight, g, mean ± 1 SD	1,484 ± 287	1,606 ± 302	1,705 ± 301	1,685 ± 206	1,772 ± 142	1,578 ± 311
Gestational age, wk, mean ± 1 SD	34.1 ± 2.9	33.3 ± 2.7	33.0 ± 2.8	32.7 ± 2.9	33.5 ± 2.2	33.0 ± 2.9
Small for gestational age	10 (53)*	12 (25)	2 (9)	2 (12)	1 (8)	26 (25)
Transported	5 (26)	18 (38)	6 (27)	3 (18)	7 (54)	30 (29)
Male sex	10 (53)	16 (33)	14 (64)	12 (71)	8 (62)	49 (47)
Labor and delivery complications	12 (63)	33 (69)	18 (82)	8 (47)	11 (85)	70 (67)
5-min Apgar ≤ 5	4/15 (27)*	2/37 (5)	3/19 (16)	0/16	1/10 (10)	10/85 (12)
Abnormal neonatal neurological examination	2 (11)	5 (10)	3 (14)	0	...	...
Acute respiratory distress	2 (11)†	11 (23)	6 (27)	11 (65)	2 (15)	36 (34)
Apnea	3 (16)	10 (21)	4 (18)	3 (18)	2 (15)	21 (20)
Weight loss > 10% birth weight	4/16 (25)	15/48 (31)	6/20 (30)	7/15 (47)	1/12 (8)	35/97 (36)
Serum bilirubin level > 10 mg/dl	11 (58)	22 (46)	11 (50)	9 (53)	8 (62)	50 (48)
Serum bilirubin level > 10 mg/dl for ≥ 3 days	5 (26)	11 (23)	10 (45)	5 (29)	6 (46)	28 (27)
Social class						
I + II, upper	0†	5 (10)	5 (23)	7 (41)	0	18 (17)
III, middle	1 (5)	7 (15)	4 (18)	2 (12)	2 (15)	15 (14)
IV + V, lower	18 (95)	36 (75)	13 (59)	8 (47)	11 (85)	72 (69)
Maternal education						
< 12 yr	12 (63)†	15 (31)	4 (18)	2/16 (12)	4 (31)	33 (31)
≥ 12 yr	7 (37)†	33 (69)	18 (82)	14/16 (88)	9 (69)	72 (69)
Maternal age ≤ 18 yr	6 (32)†	5 (10)	2 (9)	1 (6)	1 (8)	14 (13)

*$P < .05$.
†$P < .01$.

Table 3.—Follow-up Data in Relation to Newborn Head Circumference and Neurological Status

	Head Circumference at Birth, Percentile (%)				Neonatal Neurological Examination	
	< 10 (N = 19)	10-25 (N = 48)	26-50 (N = 22)	> 50 (N = 17)	Abnormal (N = 13)	Normal (N = 105)
Growth						
Height or weight < 5th percentile	5 (26)*	4 (8)	2 (9)	1 (6)	4 (31)†	8 (8)
Head circumference < 2nd percentile	5 (26)*	1 (2)	1 (5)	1 (6)	4 (31)†	5 (5)
Hearing-speech-vision						
Neurosensory hearing loss	1 (5)	0	0	0	1 (8)	0
Defective articulation	4/17 (24)	6/43 (14)	2/21 (9)	1/16 (6)	4/12 (33)†	10/96 (10)
Refractive errors, ≥ 20/70 one or both eyes	1/18 (6)	3/47 (6)	0/20	3/17 (18)	1/11 (9)	13/102 (13)
Neurological outcome						
Major abnormality	2 (11)*	2 (4)	1 (4)	0	3 (23)†	3 (3)
Minor abnormality	3 (16)*	0	4 (18)	0	0	7 (7)
Normal	14 (74)	46 (96)	17 (77)	17 (100)	10 (77)	95 (90)
Intellectual outcome						
IQ score, mean ± 1 SD	82.8 ± 15.2*	91.9 ± 14.4	91.7 ± 18.3	100.6 ± 14.4*	86.7 ± 9.6	92.2 ± 16.4
Abnormal, IQ score ≤ 70	5/17 (30)†	3/47 (6)	3/22 (13)	1/17 (6)	0/11	13/103 (13)
Borderline, IQ score 71-89	8/17 (47)†	20/47 (43)	7/22 (32)	1/17 (6)	7/11 (64)	33/103 (32)
Normal, IQ score ≥ 90	4/17 (23)†	24/47 (51)	12/22 (55)	15/17 (88)	4/11 (36)	57/103 (55)

*$P < .05$.
†$P < .01$.

neonatal neurological examinations (Table 2).

Follow-up Data

A summary of the observations made at 4 to 5 years of age in relation to neonatal head circumference and neurological status is given in Table 3.

Growth

Growth failure as defined by height or weight less than the fifth percentile was present in 12 (10%) of the 118 children studied; three of these children were microcephalic at birth, two had an abnormal neurological examination in the newborn period, and two had both abnormalities. Thus, abnormalities in growth were statistically associated with both microcephaly at birth ($P < .05$) and an abnormal neurological examination in the newborn period ($P < .01$). Five of the 12 children with growth failure were small for gestational age, but four of these five infants who were small for gestational age were also microcephalic. Microcephaly (head circumference less than the second percentile) at follow-up was also statistically associated with both microcephaly at birth and an abnormal neonatal neurological examination. No substantial relationship was observed between height, weight, or head circumference at follow-up and sex, birth weight, perinatal complications, or parental height.

Hearing, Speech, Vision

One child, who was microcephalic and had an abnormal neurological examination in the neonatal period, demonstrated a neurosensory hearing loss. Audiograms were normal in the remainder of the children. Defective articulation was noted in 14 children. This occurred in four (24%) of the children who were microcephalic at birth and nine (11%) of those who were normocephalic at birth. Furthermore, poor speech occurred in four (33%) of the children with abnormal neonatal neurological examinations and in ten (10%) of those with normal neurological examinations. The latter difference was statistically significant. There was no relationship between abnormal speech and sex, birth weight, intrauterine growth retardation, or complications of pregnancy.

No children had evidence of retrolental fibroplasia. Refractive errors, identified in 14 children, were not more prevalent in the newborn microcephalic or neurologically abnormal groups than in the remainder of the study population.

Neurological Function

Assessment of neurological function in these children at 4 to 5 years of age showed major abnormalities in five boys and one girl. Three of these children, two with spastic hemiplegia and one with diplegia and hydrocephalus, had shown evidence of neurological abnormality in the newborn period, and two of these children, one with a seizure disorder and one with diplegia and hydrocephalus, had small head measurements. An additional six boys and one girl had mild abnormalities, including five with hyperactivity and two with poor motor coordination. In this group, three had been microcephalic at birth but none had shown neurological abnormality in the early weeks of life. Major neurological abnormalities at follow-up were statistically associated with abnormal newborn neurological examinations ($P < .01$), and neurological abnormalities of all types were statistically associated with microcephaly at birth ($P < .05$ [Table 3]). Additional substantial associations were also noted between neurological abnormality and male sex ($P < .05$), a five-minute Apgar score of 5 or less ($P < .01$) and a serum bilirubin level greater than 10 mg/dl for three or more days ($P < .05$), but not with birth weight,

intrauterine growth retardation, complications of pregnancy, or socioeconomic status.

Intellectual Development

As seen from Table 3, the mean IQ score of 83 for the children who were microcephalic at birth was statistically different from the mean of 92 for children with head circumference measurements between the 10th and 50th percentiles and the mean of 101 for those with measurements greater than the 50th percentile ($P < .01$). Furthermore, five of the 17 (30%) infants with microcephaly who were studied with the Draw-a-Man test had IQ scores in the abnormally low range, ie, 70 or less, compared with seven of 86 (8%) infants with newborn head circumference greater than the tenth percentile ($P < .01$).

Although the mean IQ score of 87 for children with an abnormal newborn neurological examination was somewhat lower than the mean score of 92 for those without such a history, no statistically significant relationship was found between IQ score and newborn neurological status (Table 3).

The correlations between intellectual function and socioeconomic status and maternal education were highly substantial. Only one child from the upper (I and II) social classes had an IQ score of less than 90 compared with half the children from the lower social classes (IV and V [$P < .01$]). Similarly, significantly fewer children born of mothers with more than 12th-grade educations (33%) had IQ scores below 90 than children born of mothers with less than a high school education (76% [$P < .01$]).

COMMENT

In this follow-up study of low birth weight infants, both microcephaly at birth and an abnormal neurological examination in the neonatal period were substantially associated with poor outcome. One or both of these variables was found in 7/12 (58%) of the children with growth failure, 7/9 (78%) of the children with microcephaly, and in 5/6 (83%) of the children with major neurological deficits at 4 to 5 years of age.

Head circumference at birth also correlated with later intellectual development. The mean IQ scores for children with neonatal head circumferences less than the tenth percentile (83), between the 10th and 50th percentile (92), and greater than the 50th percentile (101) were considerably different.

Small head circumference at birth was associated with intrauterine growth retardation, low Apgar score, and poor socioeconomic status, all of which are compounding factors in the determination of direct cause and effect relationships. The decreased incidence of acute respiratory distress among infants with small head circumference may be related to intrauterine stress. Unfortunately, data on measures of perinatal asphyxia other than Apgar score are not available.

Follow-up studies of small-for-gestational-age infants have demonstrated conflicting results, in part due to the heterogeneity of this group of infants.[2] Reported studies have not generally separated growth-retarded infants whose head growth was spared from infants who were small for gestational age and who were microcephalic at birth. In the present study, outcome of the 27 infants who were small for gestational age was related to head circumference at birth. Of the ten small-for-gestational-age infants who were microcephalic at birth, four demonstrated growth failure, two were microcephalic, and two had neurological abnormalities at follow-up. In contrast, of the 17 small-for-gestational-age infants with a normal head circumference at birth, the only abnormality at follow-up was growth failure in one child. The mean IQ score for the microcephalic infants who were small for gestational age was 83 compared with 95 in the small-for-gestational-age infants with normal head size at birth.

The cause of microcephaly in our low birth weight infants is not known. During the period of active cell division, the CNS is vulnerable to a host of noxious stimuli. Malnutrition during early postnatal life is well recognized to interfere with brain cell division.[10] Such alterations in cellular growth patterns are accurately reflected in head circumference measurements during the first year of life.[11] Furthermore, head circumference at 1 year of age has been shown to correlate substantially with IQ score four or more years later.[12,13] Since the human brain undergoes the most rapid rate of cell division before birth,[14] factors that may inhibit such growth, such as maternal malnutrition, congenital viral infections, or drug usage, may produce the most pronounced effect at that time. Studies are needed to determine the precise factor or factors that effect brain growth in utero so that this high-risk group of infants can be more clearly defined.

Nonproprietary Name and Trademarks of Drug

Ampicillin sodium—*Alpen-N, Amcill-S, Omnipen-N, Penbritin-S, Polycillin-N, Principen/N.*

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Spread of *Haemophilus influenzae*

Secondary Illness in Household Contacts of Patients With *H influenzae* Meningitis

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• To determine the risk of severe secondary illness in household contacts of patients with *Haemophilus influenzae* meningitis, telephone interviews were conducted with contacts of patients with reported cases. Four probable or proved secondary cases of severe disease were identified for a secondary attack rate of 0.4%. The secondary attack rate for household contacts of patients 2 years of age and younger was 4.9%. Until safe, effective prophylactic measures become available, physicians should explain to parents that any person who becomes ill in the month after a household case of *H influenzae* meningitis should be brought to the attention of a physician for appropriate evaluation and treatment.

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Several family contacts of persons with *Haemophilus influenzae* disease have been reported to have acquired secondary cases,[1-12] but the risk of secondary cases was previously unknown. As with meningococcal disease, it has been shown that persons with close contact with a case of *H influenzae* meningitis are more likely to carry the bacteria than those without such contact.[13] To measure the risk of severe secondary disease and determine whether prophylactic measures for household contacts would be indicated, we conducted telephone interviews with contacts of patients with reported cases.

METHODS

Haemophilus influenzae meningitis is a reportable disease in Rhode Island and Minnesota. Since the late 1950s, a nurse epidemiologist from the Rhode Island State Department of Health, Providence, has reviewed hospital records on most cases and kept records of names and addresses of the patients (index patients) and results of pertinent laboratory findings, including CSF analyses and blood and CSF cultures.

Reports filed at the Minnesota Department of Health, Minneapolis, contain the names, addresses, ages, and diagnoses of the patients. Physicians have reported the evidence for the diagnoses for some cases, and the Division of Medical Laboratories, Minneapolis, has confirmed isolates of *H influenzae* for others.

For this study, illness in an index patient was considered *H influenzae* meningitis if *H influenzae* was isolated from CSF or if purulence was demonstrated in the CSF or meninges and *H influenzae* was isolated from tissue or fluid that indicated the presence of systemic infection (blood, empyema fluid, joint fluid, etc). When it was unclear from health department records whether illness in an index patient in a contacted household met this definition, we consulted hospital or autopsy records for confirmation.

The household was defined as all persons who spent at least four hours a day in the index patient's dwelling during the week before onset of his or her illness. Attempts were made to contact by telephone the households of index patients who had *H influenzae* meningitis reported between Jan 1, 1960, and Dec 31, 1975, and who resided in Rhode Island, or in Anoka, Dakota, Hennepin, Olmsted, or Ramsey counties, Minnesota (five counties that include and surround Minneapolis, St Paul, and Rochester).

The authors or health department epidemiologists interviewed parents of the child index patients or other adults in the household at the time of the reported illness who were judged to be reliable informants. Three index patients who had meningitis as adults were interviewed. We asked each informant for the following information: (1) age, sex, and relationship to the index patient of each person in the household; (2) what, if any, prophylactic medication had been given to persons in the household; and (3) whether any persons in the household had been ill during the three months before or the three months after illness in the index patient, the nature of any such illness, and whether the person received medical attention and from whom. We investigated any illness suspected of having been caused by *H influenzae* by reviewing hospital records or interviewing the contact's physician if the contact had not been hospitalized.

Secondary illness that occurred in a household contact within three months after *H influenzae* meningitis in another household member was considered to have been caused by *H influenzae* if it was proved by culture; if the illness was typical of those caused by *H influenzae* (eg, meningitis, arthritis), Gram-negative bacilli were seen in an appropriate specimen, and no organism was isolated from cultures; of if the illness was one usually caused by *H influenzae* (eg, epiglottitis, facial cellulitis) and no organism was isolated.

RESULTS

In the study period, 201 cases of *H influenzae* meningitis in 200 households were reported to the Rhode Island Department of Health, and 345 cases in 342 households in the five named counties were reported to the Minnesota Department of Health. We found telephone numbers for and interviewed informants in 103 of the Rhode Island households and 139 of the Minnesota households. The other households could not be reached by telephone; no one refused to be interviewed.

For 59 reported cases in the contacted households, the basis for diagnosis was unknown prior to the study; we determined that 37 met the stated criteria for *H influenzae* meningitis, 18 did not, and records on four could not be located. Thus, 102 contacted households in Rhode Island and 118 in Minnesota were included in the study. There were 925 contacts living in the interviewed households at the time of illness in the index meningitis patients. In addition, one index patient spent eight hours a day, four days a week, with her aunt's family of four. This brought the total number of household contacts to 929.

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Report of Cases in Household Contacts

Four proved or probable secondary cases of *H influenzae* disease occurred in household contacts of persons with meningitis. A description of these illnesses and the primary cases in the households follows.

HOUSEHOLD 1.—A 36-month-old girl became ill with a sore throat, stuffy nose, nausea, and vomiting. The next day her parents noticed that she was unsteady on her feet and irritable, shook when touched, and crawled with her neck extended. On the third day, while she became increasingly lethargic, her 24-month-old sister became ill with nausea, anorexia, crying, and intermittent lethargy. The two girls were taken to a hospital late the third day and both were found to have meningitis with *H influenzae* type b isolated from CSF.

HOUSEHOLD 2.—A 17-month-old boy became ill and was hospitalized two days later with culture-proved *H influenzae* meningitis, type unknown. His 3-month-old sister began having symptoms of meningitis two or three days after his onset and was hospitalized four days later. Gram-negative rods were seen in her CSF, but *H influenzae* was not isolated. Records of other CSF findings have been lost.

HOUSEHOLD 3.—A 19-month-old boy became ill on Dec 14, 1974, and was admitted one day later with meningitis. His CSF contained 10 mg/dl of glucose; 328 mg/dl of protein; WBCs, 1,706/cu mm, all granulocytes; and pleomorphic, skinny Gram-negative rods. *H influenzae*, type unknown, was recovered from his blood.

His twin brother had had bilateral subdural hematomas at birth, with resultant hydrocephalus. Chronic drainage was maintained with a ventriculoperitoneal shunt and he had been free of other severe illnesses. On Dec 7, he had fever and vomiting, which was treated with tetracycline and acetaminophen for three days, and his symptoms cleared in that time. On Dec 22, the child again had vomiting and fever. One day later, he was admitted to a hospital. His CSF contained 2,565 WBCs per cubic millimeter, of which 99% were granulocytes. The CSF also contained Gram-negative rods. No organisms were recovered from cultures of CSF or blood. He was treated with penicillin and chloramphenicol and was discharged improved on Jan 8, 1975.

On Jan 10, he had recurrence of vomiting and fever. The next day he was readmitted, and again, the CSF contained Gram-negative rods, but *Staphylococcus epidermidis* was isolated. He was treated with chloramphenicol, ampicillin sodium, and methicillin sodium and was discharged on Feb 21. On Feb 25, he was readmitted with symptoms and signs of meningitis, and *Escherichia coli* was isloated from the CSF. He was treated with several antibiotics and discharged on May 8.

On June 2, he was readmitted with signs and symptoms of meningitis. *Bacillus* sp was isolated from CSF, and he was treated with chloramphenicol and gentamicin sulfate. He had not had a recurrence one year later.

HOUSEHOLD 4.—A 4½-year-old boy had an upper respiratory illness beginning on Nov 18. On Nov 22, he had low-grade fever. On Nov 24, he was admitted to a hospital with meningitis, and *H influenzae*, type unknown, was isolated from his CSF.

His 5-month-old brother became febrile and irritable on Nov 25 and was admitted to the hospital. His temperature was 38.9 °C, and his left eyelid was swollen and inflamed. The CSF contained 72 mg/dl glucose, 24 mg/dl protein, and 10 WBCs per cubic millimeter, all granulocytes. No organisms were isolated from cultures of the left eye, blood, or CSF. He was treated with ampicillin for ten days and his condition quickly improved. During his course of antibiotic therapy, an epidermal cyst was removed from the left eyebrow. It did not have signs of inflammation and its relationship to the cellulitis was unknown.

Second cases of culture-proved *H influenzae* disease occurred in two other households in this study. In household 5, an 8-month-old boy had *H influenzae* meningitis 3½ weeks after his 35-month-old sister had *H influenzae* pneumonia, documented by blood culture. This second case did not follow contact with a case of meningitis. In the other household, a 48-month-old girl struck her head and, later that day, had *H influenzae* meningitis. Her sister, born 4½ months later, had *H influenzae* meningitis at age 24 days. The relationship between these two cases is doubtful because of the long interval between them.

If the first four aforementioned instances represent secondary illness caused by *H influenzae*, the overall secondary attack rate was 0.4% (95% binomial confidence limits on the mean: 0.12% to 1.11% [Table 1]). The risk for children was higher: two of the ten children younger than six months old became ill, one of the 28 children between ages six and 23 months became ill, and one child, aged 24 months, out of the 43 children two years old became ill. The risk of illness for children two years old or younger was 4.9%.

One hundred sixty-three of the 929 family members received antibiotic or sulfonamide prophylaxis or were receiving these drugs for other reasons. Most could not remember the name of the medication. All secondary cases occurred in persons who had not received prophylaxis, but the rates for those who did and did not were not significantly different ($P = .9$, Fisher's two-tailed exact test).

Risk of Secondary Disease in Household Contacts of Patients With *Haemophilus influenzae* Meningitis, Minnesota and Rhode Island, 1960-1975

Age of Contacts	No. at Risk	No. Ill	% Risk	95% Binomial Confidence Limits of Percent Risk
0-5 mo	10	2	20.0	2.5-55
0-11 mo	16	2	12.0	1.6-38
0-1 yr	38	3	7.9	1.7-21.4
0-2 yr	81	4	4.9	1.4-12.2
0-4 yr	212	4	1.9	0.5-4.8
All ages	929	4	0.4	0.12-1.1

COMMENT

Four cases in this study seem to represent serious *H influenzae* disease secondary to *H influenzae* meningitis in a household contact. Only one of the secondary cases was proved by culture, but all four are consistent

with *H influenzae* disease clinically and epidemiologically. The temporal clustering is particularly striking; all four cases occurred in the first eight days rather than throughout the three months after onsets in their contacts. It is possible that the three cases not proved by culture were caused by other agents, but that seems unlikely because it would imply that the risk of other severe disease in an eight-day period in children two years old or younger was extraordinarily high (3/81 or 3.7%).

Fifty-five percent of households with reported cases could not be contacted because current telephone numbers could not be obtained. Cases had occurred as much as 16 years before the study, mostly in young families and many had since moved. Households with secondary cases did not seem more or less likely to cooperate once they were contacted as there were no refusals. Completeness of reporting in Rhode Island during part of the study period was found to be 97.5%[14]; it was unknown in Minnesota.

The risk of secondary disease suggested by this study is similar to the 0.4% risk found in untreated household contacts of patients with meningococcal disease in endemic circumstances.[15] All secondary cases in this study and in the literature occurred in the month after meningitis in the first member of the household.[3-7,10,11] The risk of serious illness for persons in this study was 1,200 to 2,000 times the monthly risk found in several general populations[16-21]; the risk for children younger than four years old was 600 to 1,000 times the monthly risk for children of this age in general populations.[16-20] The study does not measure the risk of secondary disease for household contacts of persons with *H influenzae* illnesses other than meningitis, but the events in household 5 indicate some risk of secondary disease for contacts of persons with *H influenzae* pneumonia.

The exact risk for secondary cases cannot be calculated because of the small numbers involved and because of uncertainties about whether all four secondary cases were caused by *H influenzae*. Additional studies are needed to permit a precise estimate of the risk, but this study provides strong evidence that the risk is high enough to warrant attempts to prevent secondary disease. The pattern of spread of *H influenzae* through households is not known, and methods of preventing secondary illness have not been developed. The effects of several antibiotics on *H influenzae* in vitro have been measured,[22-27] and the penetration of some antibiotics into tears and saliva has been measured.[28] Uncontrolled studies have suggested that sulfamethoxazoletrimethoprim[29] and ampicillin sodium[30] may be useful, but controlled trials are necessary for confirmation.

Until methods of prevention have been developed, physicians should explain to parents that any person who becomes ill in the month after a household case of *H influenzae* meningitis has occurred should be brought to the attention of a physician for appropriate evaluation and treatment. Whether surveillance or preventive measures would be worthwhile after other severe illnesses with *H influenzae* is not known, but we know of no reason to believe that the secondary attack rate after other type b infections differs from that associated with meningitis.

Celia Boosalis, Gail Fahrman, Chris Sandvik, Dawn Simonson, and Ann Werhan, RN, provided assistance.

Nonproprietary Names and Trademarks of Drugs

Ampicillin sodium—*Alpen-N, Amcill-S, Omnipen-N, Penbritin-S, Polycillin-N, Principen/N.*

Gentamicin sulfate—*Garamycin.*

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Erythroid Aplasia in Juvenile Rheumatoid Arthritis

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• A 9-year old girl had clinical manifestations of juvenile rheumatoid arthritis that were further complicated by severe anemia. Subsequent studies showed the anemia to be due to erythroid aplasia. Hematologic remission was induced with prednisone, 60 mg/day.

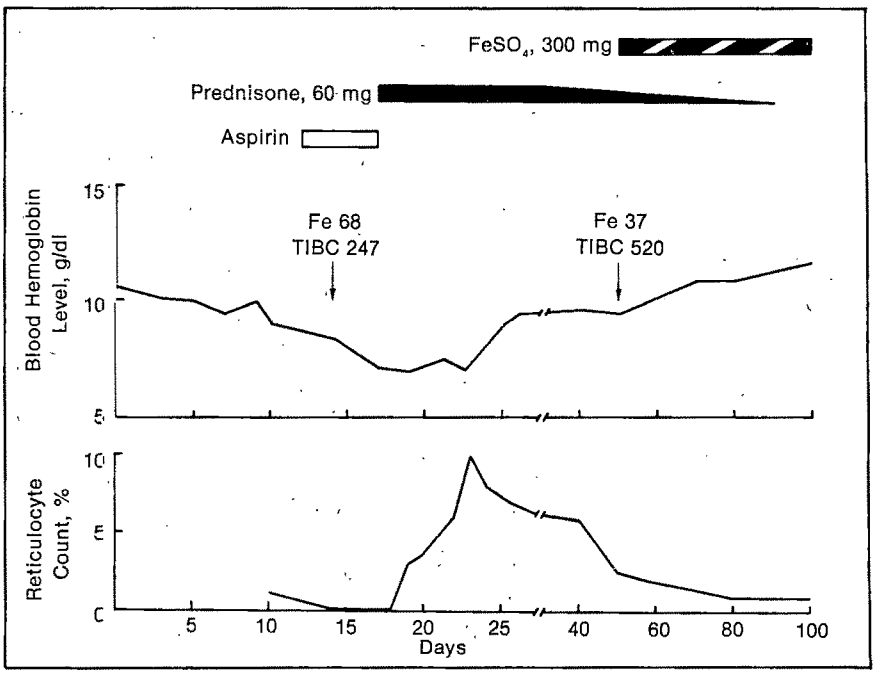
(*Am J Dis Child* 132:760-762, 1978)

Juvenile rheumatoid arthritis (JRA) is frequently associated with a moderate normocytic, normochromic anemia.[1] The major cause in most instances is the anemia of chronic inflammatory disease, but gastrointestinal blood loss that is due to salicylate therapy may contribute as well. We recently observed a patient with JRA and erythroid aplasia, as manifested by reticulocytopenia, absence of erythroblasts in the bone marrow, and normal peripheral and marrow myeloid and platelet elements. To our knowledge, this association has not previously been reported.

REPORT OF A CASE

A 9-year-old girl was admitted to Thomas Jefferson University Hospital, Philadelphia, in December 1975 for evaluation of fever and skin rash of four weeks' duration. Before the present illness, the patient had been in good health, and there was no history of recent exposure to infectious diseases, immunizations, or drugs. At the time of admission, the patient denied having cough, sore throat, neck stiffness, arthralgias, abdominal pain, dysuria, or diarrhea. Physical examination disclosed an acutely ill-appearing young girl with a temperature of 40 °C and a pulse rate of 150 beats per minute and regular. There was a patchy, nonpruritic macular eruption on the arms, legs, face, and chest. The spleen was palpable 2 cm below the left costal margin. There was no adenopathy and no hepatomegaly, and the remainder of the physical examination showed no abnormalities.

Initial laboratory studies disclosed the following values: hemoglobin, 10.8 g/dl; hematocrit, 33.4%; mean corpuscular volume (MCV), 85 cuμ; mean corpuscular



Course of blood hemoglobin level and reticulocyte count, together with medication given, and values for serum iron (Fe) and total iron-binding capacity (TIBC).

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hemoglobin count, 32%; WBC, 20,900/cu mm, with 88% neutrophils and 12% lymphocytes. Peripheral smear revealed a normal platelet estimation, normal erythrocyte morphology, and no atypical lymphocytes. Chest roentgenogram, urinalysis, and lumbar puncture showed normal findings. Cultures of urine, blood, and CSF were negative. Throat and stool culture yielded normal flora. Results of monospot test were negative, and heterophil antibody determination was normal. Antistreptolysin O titer was less than 200.

The hospital course was characterized by evening spiking temperatures of 40 °C, with wide diurnal variation to normal or subnormal levels. The evanescent skin rash persisted and was most evident during the evening pyrexic episodes. On the 11th hospital day, arthralgia of the right wrist developed, followed by painless synovial effusions of both knees. Arthrocentesis disclosed joint fluid with poor viscosity, poor mucin clot, and WBC count of 45,700/cu mm, with 97% neutrophils. Gram's stain and culture of the joint fluid were negative. Joint roentgenograms were normal. Striking neutrophilic leukocytosis persisted. Erythrocyte sedimentation rate (Wintrobe) was 63 mm/hr. Antinuclear antibody and rheumatoid factor were negative. Complement levels were normal.

The combination of high intermittent fevers, evanescent skin rash accompanying the temperature elevations, arthritis with pleocytosis of the joint fluid, and persistent peripheral leukocytosis strongly suggested the diagnosis of the systemic onset variant of JRA. Aspirin therapy was initiated and the dosage increased to 100 mg/kg/day. Slight clinical improvement occurred, but high fever and leukocytosis continued.

On the 14th hospital day, a decrease in hemoglobin level to 8.5 g/dl was noted. Results of a peripheral smear and RBC indexes were unremarkable. Reticulocyte count was .1%; serum iron level, 68 μg/dl; and iron-binding capacity, 297 μg/dl. Serum folate and vitamin B_{12} levels were normal. Results of direct and indirect antiglobulin tests were negative. Bone marrow aspiration showed virtually absent erythroid precursors, with normal myeloid and megakaryocytic elements. Reticuloendothelial iron stores were decreased but present. Hemoglobin electrophoresis disclosed primarily hemoglobin A with 2.8% hemoglobin A_2, and less than 2% hemoglobin F. Repeated stool samples were persistently negative for blood. Serum erythropoietin titer was elevated to 150 mU/ml.

By the 17th hospital day, reticulocytes were absent and the hemoglobin level had decreased to 6.9 g/dl. The combination of reticulocytopenia and absent marrow erythroblasts in the face of normal myeloid and platelet elements suggested pure erythroid aplasia. Aspirin therapy was discontinued and a regimen of prednisone, 60 mg/day, was initiated. Prompt defervescence and substantial clinical improvement occurred. A reticulocyte count of 10% developed six days after prednisone therapy was started, and the hemoglobin level increased to 9.3 g/dl. The patient was discharged on the 26th hospital day, with complete resolution of fever, rash, and arthritis (Figure).

Therapy with prednisone, 60 mg/day, was continued on an outpatient basis, with a tapering dose beginning two weeks after the time of hospital discharge. Four weeks after discharge, the hemoglobin level remained at approximately 9.0 g/dl. Repeated measurement of serum iron level was 37 μg/dl, and iron-binding capacity was 520 μg/dl. Ferrous sulfate was added because of the development of overt iron deficiency, and the hemoglobin level increased to 11.2 g/dl. Subsequently, all medications were discontinued with complete resolution of symptoms and maintenance of normal hemoglobin levels. The patient remained asymptomatic during a six-month follow-up period.

COMMENT

This patient experienced a prolonged illness of six weeks' duration, characterized by daily spiking temperatures of 39 °C to 40 °C, with intermittent afebrile periods. An evanescent nonpruritic skin rash was prominent during the episodes of high fever. Subsequently, arthralgias developed, and then, frank arthritis with inflammatory joint effusions consistent with the diagnosis of rheumatoid arthritis. Striking neutrophilic leukocytosis was present throughout the illness. This constellation of findings in a child strongly suggests the diagnosis of the systemic onset form of JRA.[2] Although several authors require the duration of disease to be at least three months before a definite diagnosis of JRA can be made,[3,4] others consider the diagnosis of the systemic onset variant of JRA after only two to three weeks.[5,6]

During the course of the illness, progressive normocytic anemia with reticulocytopenia developed. Marrow aspiration showed normal myeloid and megakaryocytic elements but a complete absence of erythroid precursors. Erythrokinetic studies were planned, but because of the child's toxic state, they could not be completed. The erythropoietin titer, although moderately elevated, did not achieve the high level characteristically associated with pure RBC aplasia.[7] Several factors may have contributed to the suppression of erythropoietin in this case. Patients with rheumatoid arthritis and anemia have been found to have erythropoietin titers inappropriately low for the degree of anemia, although the pathogenesis of this abnormality has not been explained.[8] Alternatively, certain patients with erythroblastopenia and low erythropoietin titers have shown a blocking factor to erythropoietin in their plasmas.[9] A diagnosis of pure erythroid aplasia was made,[10] and prednisone was administered in high doses. Rapid clinical improvement followed, with a return of reticulocytes and an increase in the hemoglobin concentration.

Erythroid aplasia is an uncommon disorder characterized by the absence of normoblastic proliferation in an otherwise normal marrow aspirate and consequent reticulocytopenia in the peripheral blood. The syndrome appears to be primary, or idiopathic, in nearly 50% of the reported cases.[11] Although no specific association has been identified, many of these patients have assorted immunologic abnormalities, such as antinuclear antibodies, autoimmune hemolytic anemia, hypogammaglobulinemia, or cutaneous anergy.[11] Furthermore, Krantz et al[12] have recently identified an IgG immunoglobulin in the serums of these patients that is cytotoxic to cultured marrow erythroblasts. Remissions have been achieved in several of these patients after treatment with immunosuppressive agents such as prednisone or cyclophosphamide, supporting the probable immunologic basis for this disorder in selected cases.

Wranne[13] has described a similar disorder, limited to children, of transient erythroblastopenia without a specific etiology. These patients had a brief illness and achieved spontaneous or steroid-induced remissions without long-term sequelae. The patient we describe experienced a prolonged ill-

ness consistent with JRA and subsequently, erythroid aplasia developed. The presence of this primary disorder militates against the syndrome of idiopathic transient erythroblastopenia as described by Wranne.

Congenital hypoplastic anemia, a syndrome of erythroid aplasia during early infancy, would be unlikely in our patient because of her age (9 years) and her prior normal hematologic status. Furthermore, the normal MCV and hemoglobin F level in our patient ruled out this diagnosis.[14] The anemia of chronic disease was also considered in our patient. However, this anemia is characterized by moderate anemia with hematocrit levels between 30% and 40%, essentially normal-appearing bone marrows, and normal absolute reticulocyte counts in contrast with the more severe anemia, the striking scarcity of reticulocytes, and the total absence of marrow normoblasts found in our patient.

The remaining group of patients with erythroid aplasia have a specific associated or underlying disease, the most common of which is thymoma.[15] The collagen vascular diseases, such as lupus erythematosus and other disorders of suspected autoimmune etiology, are occasionally associated with erythroid aplasia.[16] Infectious processes, including hepatitis, mononucleosis, and viral syndromes, have rarely been implicated in the etiology of this disorder.[10] In the case presented here, none of these previously identified possible causes were seen.

Erythroid aplasia has occasionally been reported in association with specific drug therapy, including aspirin, a drug administered to this patient before the onset of her illness. However, in all of the reported cases involving salicylates, multiple drugs were administered before the onset of the RBC aplasia.[17] Review of this patient's clinical course showed that manifestations of aplasia were present before the short course of aspirin therapy. In fact, the bone marrow aspiration that showed erythroid aplasia was performed less than 48 hours after the aspirin therapy was initiated. It therefore seems unlikely that the erythroid aplasia was drug related in this case.

Finally, the latent iron deficiency exposed during the recovery phase of this illness is not uncommon in other marrow failure states coexisting with and masking iron deficiency. The relapse marrow contained minimal stainable iron, thus ruling out iron deficiency as the cause for the severe anemia. However, the amount of iron was not sufficient to sustain the reticulocytosis and the increase in hemoglobin level that followed steroid therapy. Thus, supplemental iron was added.

CONCLUSION

Erythroid aplasia developed in a patient with JRA during the course of her illness. Differentiation between RBC aplasia and other causes of anemia in JRA requires accurate reticulocyte determinations and bone marrow examination. Complete remission followed prednisone therapy.

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Erythroid Hypoplasia

An Unusual Presentation of Childhood Acute Lymphocytic Leukemia

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• A 3-year-old girl had pancytopenia and bone marrow erythroid hypoplasia. The pancytopenia resolved without therapy, but the erythroid hypoplasia persisted for four months in spite of a five-week course of corticosteroid therapy. She responded briefly when androgens were added to the corticosteroid regimen, but within three weeks of stopping therapy she developed acute lymphocytic leukemia. The differential diagnosis of RBC aplasia in childhood is discussed. To our knowledge, this is the first case reported with erythroid hypoplasia as a prodrome of acute lymphocytic leukemia of childhood.

(*Am J Dis Child* 132:763-764, 1978)

Acute lymphocytic leukemia of childhood presenting as aplastic anemia with a rapid response to corticosteroid therapy was described in six children by Melhorn et al.[1] One further case has been reported recently.[2] Our report describes a patient with the unusual prodrome of RBC hypoplasia that characterized her illness four months prior to the development of acute lymphocytic leukemia.

REPORT OF A CASE

A previously healthy 3-year-old girl came to our medical center with a two-week history of irritability, anorexia, and fever, and a one-day history of left arm and left leg pain. There was no history of drug ingestion, exposure to toxins, or radiation. There was no family history of hematologic dyscrasias, and no maternal history of exposure to radiation or roentgenograms during pregnancy. Temperature was 38 °C; pulse, 154 beats per minute; respirations, 54/min. Pertinent physical findings included a grade 3/6 systolic hemic murmur. There was no lymphadenopathy or hepatosplenomegaly. No skeletal abnormalities were present. An area of cellulitis just proximal to her left ankle was present.

Laboratory studies demonstrated severe anemia and neutropenia with moderate thrombocytopenia (Table). Multiple bone marrow aspiration and bone marrow biopsy specimen showed a hypocellular marrow with erythroid aplasia, and erythroid-myeloid ratio of less than 1:500 with 0.3% blast cells, 1.1% promyelocytes, 3.2% myelocytes, 40.7% metamyelocytes, bands cells, and neutrophils, plasmacytosis, and a relative increase in mature lymphocytes (54.4%) without evidence of dyserythropoiesis. Megakaryocytes appeared to be normal in number. The fetal hemoglobin value was 0.4%; Coombs' test, antinuclear antibody, and sucrose hemolysis test were normal. Serum vitamin B_{12} and folate levels were normal; serum bilirubin level was 0.5 mg/dl. Karyotype was 46,XX with no abnormalities noted, when done both in bone marrow and peripheral blood. Urine analysis was negative for hemoglobin and hemosiderin. Red blood cell enzyme assays included low to low normal activities of aldolase (patient, 3.40; normal, 3.22 ± 49 IU/g of hemoglobin phosphofructokinase (patient, 8.30; normal, 12.6 ± 1.66 IU/g of hemoglobin, and hexokinase (patient, 0.22; normal, 0.66 ± 0.27 IU/g of hemoglobin. Glutathione peroxidase did not differ from control levels (patient, 13.5; control, 12.5 IU/g of hemoglobin). Red blood cell 2,3-diphosphoglycerate level was normal (patient, 4.9; normal, 3.6-5.8 μmole/m of RBCs). Chest and skeletal roentgenograms and bone scan were normal.

Material aspirated from the area of cellulitis grew *Staphylococcus aureus*, and treatment was instituted with a ten-day course of nafcillin and gentamicin. The patient was transfused with leukocyte-poor RBCs. On the fourth hospital day her platelet count rose to $162 \times 10^3/\mu l$ and remained normal thereafter. Repeated bone marrow aspirate and biopsy specimen on day 14 showed improved cellularity with normal number of myeloid precursors and megakaryocytes but persistent erythroid hypoplasia.

By the 28th day, the peripheral neutrophil count had risen to greater than 1,500/μl. However, severe anemia persisted and bone marrow examination continued to show erythroid hypoplasia in the presence of normal myeloid elements and megakaryocytes. The diagnosis of RBC aplasia was made and prednisone therapy was started, 40 mg/sq m/day. However, the hemoglobin level continued to drop, requiring further RBC transfusions (Table). After five weeks of prednisone therapy, androgen therapy (oxymetholone, 2 mg/kg/day) was added. Within three weeks, the patient experienced reticulocytosis and a rise in hemoglobin level (Table). In the 14th week of illness, the doses of androgen and corticosteroid were gradually reduced over a four-week period. Six weeks later, and two weeks after stopping all therapy, the patient's hemoglobin level decreased and she developed neutropenia (Table).

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Hematologic Changes During Illness								
	Normal Range	4/2/76	4/29/76*	5/20/76	6/3/75†	6/24/76	7/8/76	8/19/76
Days after Presentation		1	28	49	63	84	98	140
Hemoglobin, gm/dl	11-16	4.1 (9.0)‡	5.8	4.1 (8.4)‡	7.3	7.9	9.9	7.8
MCV, femtoliters	74-86	76	77	85	84	99	106	99
WBCs × $10^3/\mu l$	4.3-10	2.6	6.8	11.6	7.2	6.2	8.5	6.1
Absolute PMNs × $10^3/\mu l$	1.83-7.25	0.4	1.77	7.77	2.52	4.74	6.04	0.55
Absolute reticulocytes × $10^3/\mu l$	25-75	0.0	0.0	0.0	0.0	164.0	3.0	0.0
Platelets × $10^3/\mu l$	150-450	87	756	645	725	768	675	468
Erythroid-myeloid ratio (marrows)	1:2.6	1:500	1:25			3:1		1:3

*Prednisone therapy begun.
†Androgen therapy begun.
‡Posttransfusion value.

Bone marrow examination showed a hypercellular specimen with 91% lymphoblasts with large PAS-positive granules and negative myeloperoxidase and Sudan black B stains. T- and B-cell typing disclosed 90% null cells. The diagnosis of acute lymphatic leukemia was made and therapy instituted with standard chemotherapy.

Remission was maintained for 11 months when neutropenia developed and bone marrow examination demonstrated 49% lymphoblasts. A second remission was induced with vincristine sulfate, prednisone, l-asparaginase, and doxorubicin hydrochloride. This remission lasted four months, but the patient relapsed and has now only achieved partial remission with doxorubicin therapy.

COMMENT

This patient had pancytopenia associated with infection that progressed to erythroid hypoplasia four months before acute lymphocytic leukemia developed.

Red blood cell aplasia is a distinct hematologic entity characterized by anemia and reticulocytopenia, with bone marrow erythroid aplasia or hypoplasia in the presence of normal myeloid and megakaryocytic elements. The differential diagnosis of this entity includes congenital hypoplastic anemia (Diamond-Blackfan syndrome), transient erythroblastopenia of childhood, and acquired pure RBC aplasia. Wang and Mentzer[3] found several clinical and laboratory variables helpful in differentiating congenital hypoplastic anemia from transient erythroblastopenia of childhood. Acute onset of illness, normal fetal hemoglobin value, a normal mean corpuscular volume (MCV), and low to low normal levels of the RBC enzymes lactic dehydrogenase, glyceraldehyde 3-phosphate dehydrogenase, aldolase, phosphofructokinase, transaminases, and glutathione peroxidase characterized transient erythroblastopenia of childhood.

Acquired pure RBC aplasia has been associated with thymoma, hypogammaglobulinemia, paraproteins, antinuclear antibodies, solid tumors, hemolytic anemia, toxins, drugs, infection, malnutrition, and leukemia during maintenance chemotherapy.[4,5] It is mainly a disease of late childhood and adulthood.[6] In addition, there have been several well-documented cases of leukemia developing in adult patients with acquired pure RBC aplasia.[5,7] The leukemia is usually of the acute myelocytic variety, although patients with chronic myelocytic,[6] monocytic,[8] and chronic lymphocytic leukemia[9] have been described. Recently, a patient developing acute lymphocytic leukemia in the course of therapy for congenital hypoplastic anemia had been described.[10]

Our patient had pancytopenia and infection. Within a few days, the myelocytic and thrombocytic elements resolved. Fetal hemoglobin value, MCV, serum folate level, and vitamin B_{12} concentration were normal. Red blood cell enzymes were consistent with transient erythroblastopenia of childhood.[3] Her anemia persisted for three months despite a five-week course of corticosteroid therapy. Therapy with oxymetholone and corticosteroids caused a brief response, but this was soon followed by the leukemic phase of her disease. Of note is that immediately prior to the development of the leukemic phase of the illness, an increase in MCV was noted that could not be explained on the basis of concomitant reticulocytosis alone. This finding is not uncommon in the preleukemic phase of adult myelogenous leukemia.[11] To our knowledge, this is the first patient reported who has developed childhood acute lymphocytic leukemia following a prodrome of RBC hypoplasia.

James A. Stockman III, MD, helped prepare this article.

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Aseptic Necrosis After Renal Transplantation in Children

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• Aseptic necrosis developed in 11 (6%) of 171 recipients of renal allografts who underwent transplant operations at Childrens Hospital of Los Angeles between February 1967 and August 1977. Pain was the predominant presenting symptom and preceded roentgenographic evidence of aseptic necrosis by as long as seven months. Initial symptoms occurred two months to four years posttransplant.

Limited weight bearing and reduction in the dosage of prednisone failed to prevent the progressive destruction of five femoral heads in three patients. Hip replacement led to an amelioration of the symptoms and a resumption of normal activity in each patient. Two patients with involvement of multiple osseous structures have persistent knee and elbow joint pain and effusions, and one of them has required prosthetic replacement of the proximal humerus. No therapy was required for patients with aseptic necrosis of single bones of the hand and foot.

There was no statistically significant difference in the total steroid dose received during the first posttransplant year between patients in whom aseptic necrosis developed, and those in whom it did not develop.

(*Am J Dis Child* 132:765-767, 1978)

Aseptic necrosis occurs in patients receiving corticosteroids for various disease states and in recipients of renal allografts. In the latter patients, corticosteroid therapy as well as preexisting renal osteodystrophy,[1,2] hypercalcemia,[3] and hypophosphatemia[1] have been implicated etiologically.

In adult recipients of allografts the incidence of aseptic necrosis has varied between 4% and 37%.[1,2,4-19] There is no previous report that gives details of aseptic necrosis in pediatric recipients of renal allografts. However, in the previous reports concerning renal transplantation in children,[20-25] aseptic necrosis has been mentioned as a complication with an incidence of 0% to 9%.

This report relates our experience with aseptic necrosis in 171 pediatric recipients of allografts in whom transplantation took place at Childrens Hospital of Los Angeles.

MATERIALS AND METHODS

Between February 1967 and August 1977, 171 children with end-stage renal disease received 227 renal allografts from 42 live-related donors, four live-unrelated donors, and 181 cadaver donors. All of the live-related donors and the live-unrelated donor grafts were first transplants, whereas 120 of the cadaver donor grafts were first transplants, 47 grafts were second, 11 grafts were third, and three grafts were fourth.

Immunosuppressive therapy consisted of azathioprine and prednisone as previously described.[5] Antithymocyte globulin was used since August 1976, in 13 patients receiving a cadaveric renal allograft in a randomized trial. No patient underwent thymectomy and only one patient underwent splenectomy prior to a second transplant. Graft rejection was initially treated by increasing the oral dose of prednisone; since 1971, it was treated by intravenous methylprednisolone therapy (30 mg/kg/day for three days).

A serial roentgenographic evaluation of osseous structures (hands, hips, and knees) was obtained routinely prior to initiating dialysis, at six-month intervals during the course of dialysis, at the time of transplantation, at six months, at one year after transplantation, and yearly thereafter. If the patient complained of bone or joint pain after transplantation, roentgenograms were obtained and if abnormalities were noted, serial studies were ordered.

RESULTS

Incidence

Of the 171 patients, clinical and roentgenographic manifestations of aseptic necrosis developed in 11 of them (6%) after transplantation. The age of those affected at the time of transplantation was between 6½ and 18 years. Five of the 11 patients were pubertal at the time of transplantation; six were male and five were female. Three patients were recipients of a live-related donor graft and eight were recipients of a cadaver donor graft; three of the latter category received their second grafts.

Bones Involved

In two patients multiple bones were involved, including both femoral heads. In two patients one femoral head was involved; in four, both distal femurs were involved; in one, the talus was involved, in one, the tarsonavicular was involved, and in one, the carpal navicular bone was involved.

Symptoms

Pain was the predominant symptom and it preceded roentgenologic evidence by as long as seven months. Joint effusions were clinically apparent in almost all of the patients with aseptic necrosis of the knees and elbows. The symptoms occurred two months to four years posttransplant.

Roentgenographic Findings

Roentgenographic changes depended on the location of the aseptic necrosis. Aseptic necrosis of the femoral and humeral heads pursued a similar course roentgenographically. The earliest sign was the appearance of a

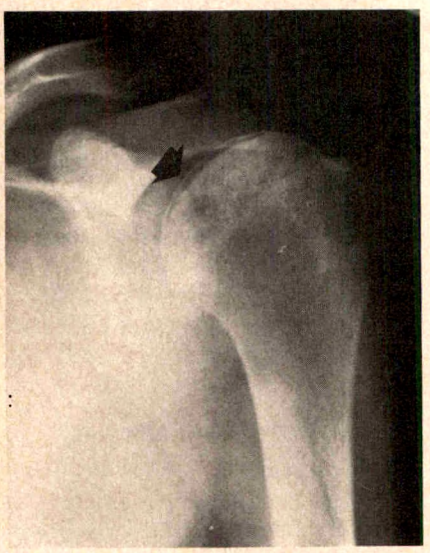
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thin, subcortical radiolucent line, paralleling the articular surface (Figure). This was followed by sclerosis, cyst formation, flattening, and progressive destruction. In the other locations, sclerosis and not the subcortical radiolucent line was the earliest change, and it was followed by cyst formation, flattening, and progressive destruction.

Therapeutic Approach

In eight of the 11 patients, no specific therapy was instituted and mild oral analgesics were administered for relief of pain. Roentgenologic evidence of healing in association with reduction in symptoms was seen in two patients with bilateral involvement of the knees (within 12 to 34 months). Three patients had progressive destruction of femoral heads and humeral head secondary to aseptic necrosis, with incapacitating pain necessitating replacement of the heads despite a lowering of prednisone dosage and limited weight bearing. One patient with multiple involvement of the bones had bilateral total hip replacement and replacement of the left humeral head with excellent functional results and amelioration of symptoms. The other patient with multiple involvement of the bones underwent bilateral femoral head replacement, followed by total hip replacement on the left, also with good results. The third patient needed unilateral total hip replacement for progressive destruction. This was the only area involved.



Aseptic necrosis of humeral heads. Arrow indicates subcortical radiolucent line paralleling the articular surface.

Pathological Condition

Five femoral heads and one humoral head were available for examination. All tissues showed the same lesion, namely, a nonspecific synovitis with fibrous and connective tissue replacing the necrotic bone. There was no vasculitis; however, the media of some vessels was thickened. No fat emboli were seen occluding blood vessels.

Predisposing Factors

Corticosteroids.—Since the highest dosage of corticosteroids is administered during the first year after transplantation, we compared the prednisone dosage of eight of the 11 patients with aseptic necrosis who were more than one-year posttransplant with that of 62 recipients who had a functioning graft for at least one year and had no clinical and/or roentgenologic evidence of aseptic necrosis. There was no statistically significant difference between the two groups (Table).

Osteodystrophy.—All of the patients with aseptic necrosis had roentgenologic evidence of osseous disease prior to transplantation. In six patients, the abnormalities were limited to variations in bone density. The five remaining patients had roentgenologic evidence of secondary hyperparathyroidism while receiving dialysis. Serum parathormone determinations were not routinely performed on all patients until recently.

The serum calcium level was normal range (9 to 11 mg/dl) in the affected patients for at least a six-month period prior to the onset of aseptic necrosis. The serum phosphorus levels were not different from those of the unaffected recipients with a comparable degree of graft function.

COMMENT

Clinical and/or roentgenologic evidence of aseptic necrosis occurred in 11 of 171 patients (6%) who received a renal allograft at the Childrens Hospital of Los Angeles during a 9½-year period. This incidence is similar to that previously reported in pediatric recipients[20-25] and it is comparable to that reported in adult recipients.[1,2,4-18,26]

Although corticosteroids have been implicated in the pathogenesis of aseptic necrosis, the relationship remains equivocal. Fisher and Bickel[27] reported aseptic necrosis involving one or both femoral heads in 77 patients receiving corticosteroids, only one of whom was a recipient of an allograft. Harrington et al[11] noted a sharp decrease in the incidence of aseptic necrosis in those patients receiving a lower dose of corticosteroids during the initial three weeks after transplantation. Similarly, Smyth and Leidholt[14] noted a decrease in the incidence of aseptic necrosis in patients receiving a lower dosage of corticosteroids in conjunction with antilymphocyte globulin therapy. However, Troch et al[15] were unable to show a substantial difference in the amount of prednisone received from the time of transplantation to the time of diagnosis in a group of recipients with aseptic necrosis compared to a control group of unaffected recipients observed for the same time interval. Similarly, neither Cruess et al,[6] Briggs et al,[1] nor Bewick et al[18] were able to show an association between the total dose of prednisone and the development of aseptic necrosis in adult allograft recipients.

We compared both the total dose of prednisone received during the first posttransplant year and the dose of prednisone related to the recipient's weight of eight affected patients who were more than one-year posttransplant with that of a control group of 62

Relationship of Prednisone Dosage During First Posttransplant Year and the Development of Aseptic Necrosis

Group	No. of Patients	Prednisone Dosage	
		mg/kg/mo, Mean ± SD	g/yr, Mean ± SD
Aseptic necrosis	8	29.5 ± 0.20	17.6 ± 0.37
Control	62	29.0 ± 0.49	17.0 ± 0.70
Significance	. . .	$P > .75$	$P > .75$

patients who survived at least one year with a functioning graft. There was no substantial difference between the two groups of recipients.

Fat embolism induced by corticosteroids has been considered by many authors[2,5,6,9,27,28] in the pathogenesis of aseptic necrosis. Fisher and Bickel[27] examined, histologically, 14 femoral heads involved with aseptic necrosis from patients receiving corticosteroids who were not transplant recipients. Fat emboli were seen in ten specimens. However, Bravo et al,[5] Evarts and Phalen[9] and Cruess et al,[6] all of whom considered fat emboli as the most likely cause for aseptic necrosis in recipients of allografts were unable to confirm their hypothesis by microscopic examination of the involved osseous tissue. Similarly, we were unable to show fat emboli in the six specimens available for study. Since recipients of renal allografts have hyperlipidemia,[29] and since systemic fat embolization occurs after transplantation,[19] such a hypothesis seems plausible. Unfortunately, the data have not been confirmatory.

An additional complication of corticosteroid therapy, namely, osteoporosis, has been proposed by Cruess et al[6] as a factor predisposing to aseptic necrosis in recipients of allografts. In our experience, osteoporosis occurs frequently after transplantation and the incidence was not higher in the recipients with aseptic necrosis compared to a control group of 30 patients matched for renal function and age.

The presence of unresolved secondary hyperparathyroidism has been proposed by Briggs et al[1] as predisposing to the development of aseptic necrosis after transplantation. Eight of the 11 affected patients studied by Briggs et al[1] had roentgenologic and/or histologic evidence of secondary hyperparathyroidism prior to transplantation. The report by Griffiths et al[2] supported the relationship; however, Troch et al[15] excluded the possibility since none of their patients with aseptic necrosis after transplantation had preexisting hyperparathyroid bone disease. Five of the patients in our series had roentgenologic evidence of secondary hyperparathyroidism prior to transplantation, including all four recipients with involvement of the femoral heads. The mechanism by which preexisting secondary hyperparathyroidism may predispose to aseptic necrosis is unknown; both hypercalcemia and hypophosphatemia have been implicated. Briggs et al[1] noted a substantially higher mean serum calcium level and a substantially lower mean serum phosphorus level six to eight months posttransplant in those recipients with aseptic necrosis. In addition, Chatterjee et al[3] reported aseptic necrosis of the femoral head in seven to 16 posttransplant patients (43.7%) with hypercalcemia, whereas only three to 44 recipients (6.9%) without hypercalcemia were affected. No mention was made of the serum phosphorus levels in the latter report. Neither hypercalcemia nor substantial hypophosphatemia was present in our affected patients. Although corticosteroids may be an important factor in the development of aseptic necrosis,[27,30] it is impossible to implicate a single etiologic factor in the pathogenesis of aseptic necrosis in renal allograft recipients.

Neither limitation of weight bearing nor reduction in the dose of prednisone have curtailed the progressive destruction of the femoral heads. Persistent pain and impaired ambulation have necessitated surgical replacement of the hip joint. In our limited experience, this has proved beneficial and we now consider total hip replacement as the treatment of choice in patients with progressive aseptic necrosis of the femoral heads. Involvement of single bones other than the femoral heads does not require any specific therapeutic intervention.

Nonproprietary Name and Trademark of Drug

Azathioprine—*Imuran.*

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Effect of Prednisone on Growth and Bone Mineral Content in Childhood Glomerular Disease

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• **Children with acquired glomerular disease were divided into two groups: Group 1 patients received short-term daily or long-term alternate-day prednisone (up to 2.7 mg/kg/48 hr); group 2 patients received no corticosteroids. Height, bone mineral content (BMC), and bone density were evaluated in the two groups and compared to those of 800 sex- and age-matched controls; BMC and bone density were assessed by the photon absorption technique.**

Significant demineralization was present in 18 of 25 prednisone-treated and none of the 17 nonprednisone-treated patients ($P < .001$). Group 1 patients were 5.3 ± 0.7% shorter than controls, while group 2 patients were only 1.9 ± .8% shorter ($P < .02$). Height velocity was 2.6 ± 0.8 cm/yr in group 1 and 5.1 ± 0.8 cm/yr in group 2 patients ($P < .05$). When prednisone therapy was discontinued, six patients had an increase in height and BMC toward normal values.

This study suggests that BMC and height velocity are correlated. Both appear to be influenced by alternate-day prednisone therapy rather than by glomerular disease per se.

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Bone mineral content (BMC) can be assessed by the relatively simple, noninvasive technique of direct photon absorptiometry, which measures the attenuation by bone of a highly collimated low energy photon beam.[1] This method has been used to monitor the extent of skeletal demineralization in renal disease in adults[2-4] and in children.[5] Using this technique, we found that demineralization in children with primary glomerular disorders was confined mainly to those receiving prednisone therapy. Our intent in this study is to investigate in greater detail a larger population of children with glomerular disease over a longer period of time and to examine the relationship of prednisone therapy to linear growth, BMC, and bone density.

Patients treatment with glucocorticoids may develop osteoporosis or decreased bone mineralization.[6] Daily glucocorticoid administration possibly inhibits bone formation, stimulates bone resorption, and prevents linear growth.[7] Alternate-day corticosteroid therapy has been used in nephrotic children because it permits growth but suppresses disease activity.[8,9] A recent study in young rabbits compared the effects on bone growth and bone mineral content of daily vs alternate-day corticosteroid administration.[10] Bone growth, epiphyseal width, calcium retention in bone, and bone mineralization was similar in control and alternate-day corticosteroid-treated animals. Daily corticosteroid therapy prevented growth and led to bone demineralization. We decided to compare the growth and bone mineral content of corticosteroid-treated children with glomerular disease, mainly receiving long-term alternate-day therapy, to patients with similar diseases not receiving prednisone.

PATIENTS AND METHODS

Photon Absorptiometry

Bone mineral content is determined by absorptiometric measurements with a beam of low-energy gamma radiation from a monoenergetic radionuclide source (iodine 125 at 27.4 keV). Changes in transmitted beam intensity are related to the attenuation by bone mineral, and the integrated attenuation is proportional to the mass of bone mineral in the scan path. This technique can also evaluate the bone width (BW). Repeated measurements are within 2% to 3% of each other,[11] and scans accurately indicate the ash weight of the bone to within 1% to 3%. Measurements at a single site in various long bones correlate highly ($r = .95$) with the weight of that long bone, the total skeletal weight, and total body calcium concentration.[12-14] These correlations also hold for patients with renal disease.[15]

Measurements of photon absorption were made using a direct readout system,[16] and the instrument was calibrated at least once daily. The BMC, BW, and their ratio, BMC/BW (roughly indicative of bone density), were determined on the radius and ulna shafts at a point one third of the forearm length proximal to the ulnar styloid. Four to five determinations were made at each site and the average value

used. The radiation dose to the forearm from these measurements was found to be under 10 mrem (compared to the International Commission on Radiological Units' maximum permissible dose of 7,500 mrem to the limbs). Careful shielding prevents gonadal irradiation.

Normal Population

Absorptiometric determinations were made on radius (N = 768), ulna (N = 833), and humerus (N = 674) of healthy school age children from Dane County, Wisconsin. Values for these children were presented elsewhere.[17] The children were of normal height and weight compared to US standards for whites.

In order to evaluate skeletal status of patients, we established multiple regression equations for normal children that predicted an expected BMC of each bone, taking into account height, weight, age, sex, and BW as independent variables. The measured BMC in each patient was compared to the expected BMC predicted for that patient. The multiple correlation coefficients were approximately .94 and the standard errors of estimate were 10.6%, 8.6%, and 13.1% for the humerus, radius, and ulna, respectively. Standard errors of estimate were expressed as a percentage to account for age differences in bone size. Similar regressions were established for BW and for the BMC/BW ratio. Since the standard deviation averaged about 10%, a decline of 20% or more was considered to indicate significant demineralization.

Patient Population

Forty-two children (19 boys and 23 girls), aged 3 to 18 years (group 2), treated in the Pediatric Renal Disease Clinic of the University of Wisconsin, were evaluated. Informed consent was obtained from the patients or their parents.

Patients had measurements of BMC, BW, and the BMC/BW ratio on the distal radius and ulna of the nondominant arm. Several patients had measurements made at six-month intervals for periods as long as two years, so that four to five measurements were available. The patients, aged 3 to 17 years (group 1), with primary glomerular disease had been treated with prednisone for 1 to 16 years (mean, 4.8 years). One patient was treated with prednisone for three days each week. Six patients developed edema and proteinuria and were treated with prednisone daily for four to eight weeks during the course of the study, but then were retreated with alternate-day therapy. The remaining 19 patients were treated with alternate-day prednisone only. Six patients discontinued corticosteroid therapy during the study. The diagnoses in these patients were as follows: minimal lesion nephrotic syndrome, 15 cases; membranoproliferative glomerulonephritis, three; systemic lupus erythematosus, four; Wegener's granulomatosis, one; and focal sclerosing glomerulonephritis, two. Group 2 consisted of 17 patients, aged 4 to 18 years, not treated with prednisone during the course of the study. The diagnoses were as follows: minimal lesion nephrotic syndrome, four cases; membranoproliferative glomerulonephritis, seven; systemic lupus erythematosus, two; chronic glomerulonephritis secondary to Wegener's granulomatosis, one; chronic crescentic glomerulonephritis, two. Two children with minimal lesion nephrotic syndrome developed transient edema and five of the seven children with membranoproliferative glomerulonephritis had intermittent edema, but these patients were not treated with prednisone. Salt restriction and furosemide or hydrochlorothiazide was sometimes used to treat edema.

Specific diagnoses were established by a combination of typical clinical features, and by percutaneous renal biopsy in 30 patients. Patients with a history of nephrotic syndrome responsive to prednisone in a dose of 60 mg/sq m/day for four weeks were presumed to have the minimal lesion nephrotic syndrome[18] and did not have a renal biopsy performed.

Standing height, using a stadiometer, and weight were measured by the same nurse on each visit.

Analysis

The differences between groups were compared by Student's t test or χ^2 analysis.

RESULTS

Bone Mineral Content

Fifty-nine measurements in the 25 group 1 patients and 38 measurements in the 17 group 2 patients were made. These patients had similar diseases, and serum creatinine concentrations were comparable (1.0 ± 0.8 mg/dl [SD] in group 1 and 1.0 ± 0.5 mg/dl in group 2 patients). Significant demineralization (> −2 SD) was found on at least one measurement in 18 of 25 group 1 patients and in none of 17 group 2 patients ($P < .001$). The average BMC/BW ratio in group 1 patients was 16.7 ± 1.2% lower than matched control values (mean ± SE) in contrast to 7.9 ± 1.2% lower in group 2 patients ($P < .001$). The single lowest value for each patient showed a reduction in BMC/BW of 20.1 ± 1.7% in group 1 vs 10.7 ± 1.3% in group 2 patients ($P < .01$).

The BMC/BW ratio was evaluated at several prednisone dosage schedules. The average ratio for those taking 5 to 15 mg of prednisone every other day was 9.2 ± 2.8% lower than that of controls; for those taking 15 to 30 mg every other day, it was 18.0 ± 4.1% lower, and the value for > 30 mg every other day was 18.4 ± 1.4% lower. The extent of reduction in the BMC/BW ratio was significantly greater ($P < .05$) in patients treated with > 30 mg of prednisone than in those treated with 5 to 15 mg of the drug. However, when the dosage schedule in milligrams per kilogram per day was compared over a wide range of values, no significant differences in BMC or the BMC/BW ratio were apparent. The values for BMC/BW were as follows: < 0.5 mg/kg/48 hr, 14.7 ± 2.2% (SE) reduction from control means (mean ± SEM); 0.5 to 1.0 mg/kg/48 hr, 14.9 ± 1.4% reduction; 1.0 to 1.5 mg/kg/48 hr, 19.8 ± 2.7% reduction; and 1.5 to 2.3 mg/kg/48 hr, 19.7 ± 2.4% reduction.

Influence on Height Achievement

Group 1 patients were 5.3 ± .7% shorter than control mean subjects (SE) whereas group 2 patients were 1.9 ± .8% shorter ($P < .02$). One Vietnamese girl was excluded from this height evaluation because we had no appropriate standards for comparison. The individual values for height achievement and for BMC/BW ratio (Fig 1) indicate that group 1 patients were shorter and more demineralized than group 2 patients. The influence of prednisone and influence of demineralization on height achievement was examined. Greater reduction in height was found with reduced bone mineral content. In addition, at each range of BMC/BW ratio values (0% to 10% and 10% to 20% reduction), patients in group 1 were shorter than group 2 patients.

Group 1 patients were 7.3 ± 19.7% (SD) heavier than control subjects, whereas group 2 patients were only 1.9 ± 15.6% heavier ($P < .05$).

Patients treated with the highest

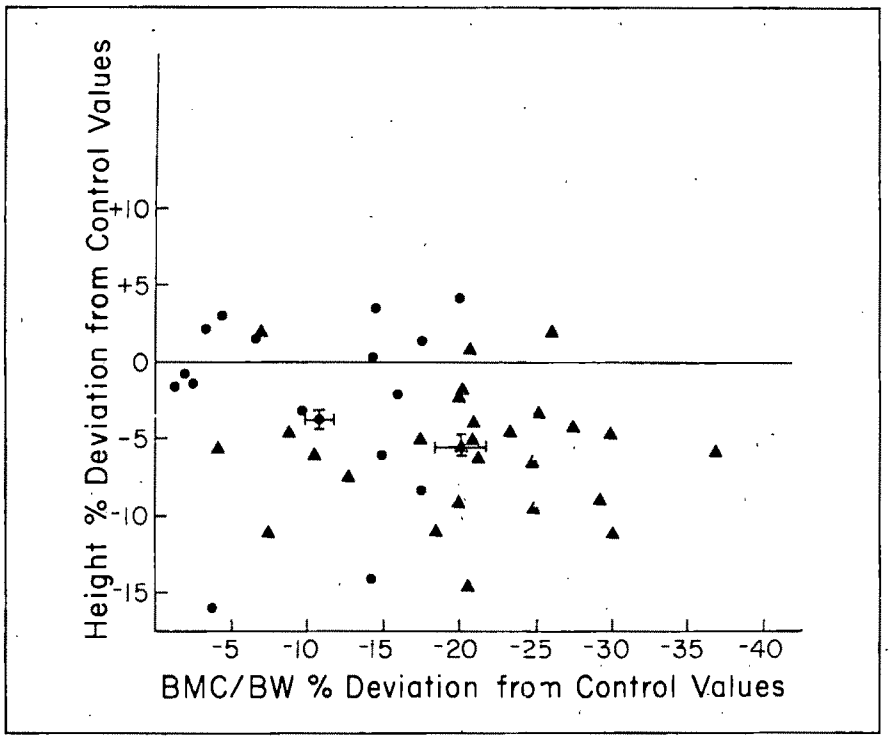


Fig 1.—Relationship of height to BMC/BW ratio. Mean ± SEM (brackets) for each group are shown. Differences in height achievement and BMC/BW ratio between groups are significant. Triangles indicate group 1 patients; circles, group 2 patients.

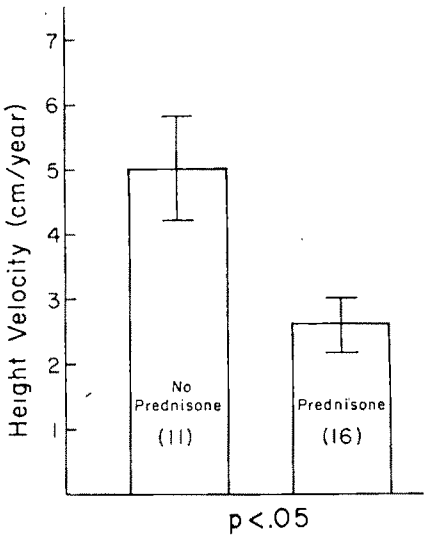


Fig 2.—Height velocity in those patients followed up for more than 12 months (at which point velocity can be accurately evaluated). Each bar represents mean ± SD of values from each group. Those patients (N = 16) treated with prednisone were significantly shorter than nonprednisone-treated patients (N = 11).

doses of prednisone were the shortest. With a dose of 0.5 mg/kg/48 hr, a 5.5 ± 1.0% (SE) height reduction from control values was found; with 0.5 to 1.0 g/kg/48 hr, a 3.3 ± 0.9% reduction; 1.0 to 1.5 mg/kg/48 hr, a 4.9 ± 1.2% reduction; and with 1.5 to 2.3 mg/kg/48 hr, a 10.9 ± 2.2% reduction. This last value differs significantly from those found with lower prednisone doses ($P < .05$) or in group 2 patients or controls ($P < .01$).

Influence on Height Allowing for Height of Parents

Most standards for the height attained by a certain age fail to account for parental stature. Standards are available for prepubescent children up to age 9 years allowing for the height of both parents.[25] Although many of our patients are adolescents, three group 1 patients and five group 2 patients were young enough to be analyzed. Two of the group 1 patients were at the third percentile and the other was less than the third percentile in relation to their parent's heights. The group 2 patients ranged from the 25th to 75th percentile.

Changes in Height Velocity

Serial height measurements for periods of at least 12 months were available in 16 of 25 group 1 and 11 of 17 group 2 patients. Height velocity in these patients was 2.6 ± 0.4 cm/yr (SD) in group 1 and 5.1 ± 0.8 cm/yr in group 2 patients (Fig 2). Hence, group 2 patients grew at a significantly faster rate ($P < .05$). Since velocity varies with age, the individual growth velocity values, both for boys and girls, are shown on standard height velocity curves[26] (Fig 3). Height velocity is greater in boys not treated with prednisone. In some group 1 patients, growth velocity is < 10% for age. Interestingly, three girls more than 16 years old appear to be growing at an age when most girls have stopped growing. This growth after age 16 in each girl was associated with the cessation of daily prednisone dosage and the resumption of an alternate-day schedule at a time prior to the onset of this study.

When the height increase in centimeters per year (velocity) is compared to the change in BMC, an increasing ratio was highly associated with an increase in height velocity (by linear regression, $r = .77$, $P < .01$) in group 2 patients. No association was found between these two variables in group 1 patients. Two patients in group 2 had been treated with prednisone in the year prior to the initiation of our studies, but were not receiving prednisone when our initial measurements were taken and had a sizable increase in bone remineralization and height velocity during the year after prednisone was stopped. As anticipated, in group 1 patients the greatest height gain was associated with reduction of prednisone dose from 40 to 10 mg every other day in two patients, stopping therapy altogether in one patient, and going from daily to alternate-day doses in two patients.

Changes Associated With Discontinuation of Prednisone Therapy

Prednisone therapy was discontinued in five patients during the course of the study. The subsequent increase in bone density and height in each patient is shown in Fig 4. A compara-

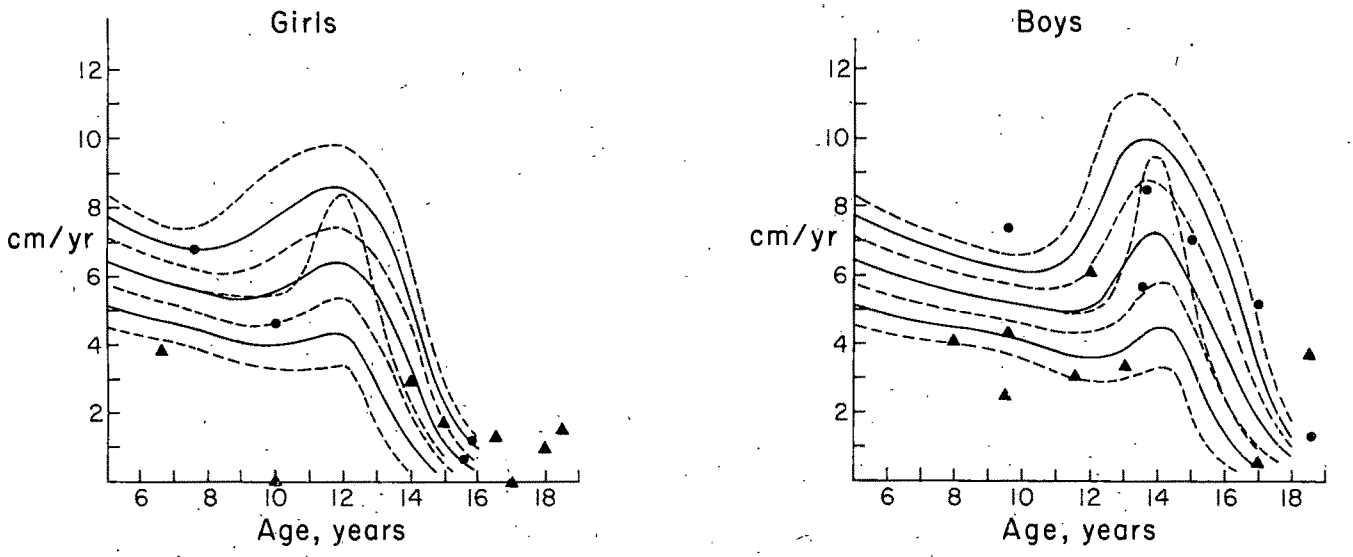


Fig 3.—Height velocity (centimeters per year) in relation to patients' age in years in girls (left) and boys (right). Each point represents growth in previous 12 months. Triangles indicate group 1; circles, group 2. Lines represent, from top to bottom, 97th, 90th, 75th, 50th, 25th, 10th, and 3rd percentiles. Chart is based on data of Tanner et al.[26] Growth in boys and girls after age 18 is found in patients changing from daily to alternate-day prednisone therapy.

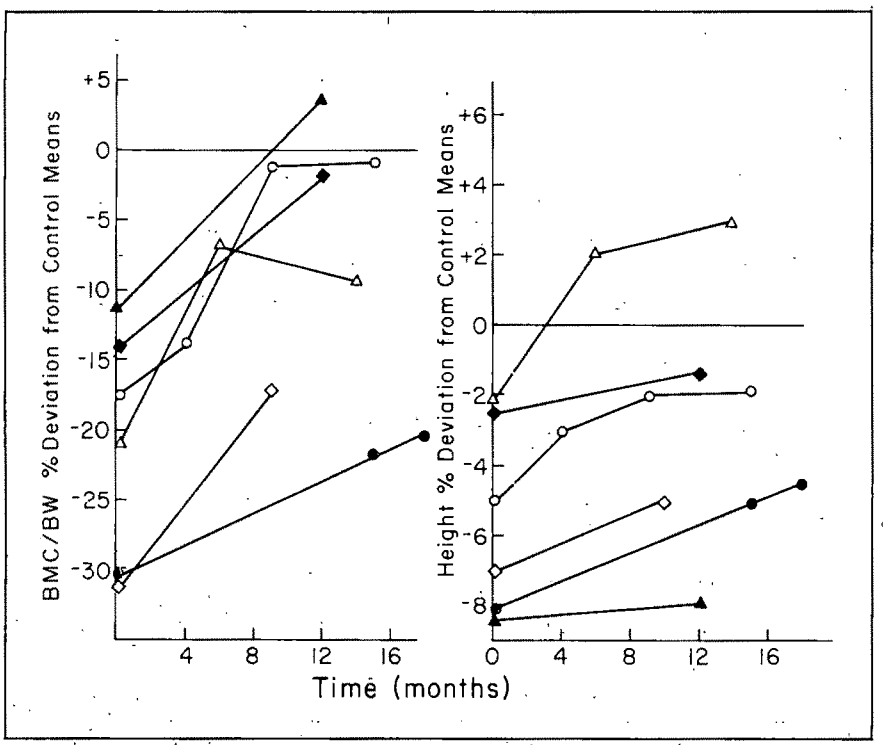


Fig 4.—Changes with time in BMC/BW ratio and height after prednisone therapy was discontinued. Patient designated by solid triangle has closed epiphyses and therefore did not grow. Other patients were younger.

ble increase in BMC was also noted. In one patient, a girl aged 18 with closed epiphyses, growth was minimal. The influence of prednisone on growth and bone mineral content, therefore, appears to be reversible within a few months.

COMMENT

This study has examined children with glomerular disease for a period of time sufficient to evaluate the influence of prednisone on growth velocity and on serial measurements of BMC/BW ratio as an indicator of bone density. A comparison was made between patients with the same disease type, of a similar age, and with comparable serum creatinine values. Patients having glomerular diseases in which prednisone would not ordinarily be used, such as Berger's IgA-IgG nephropathy, Henoch-Schönlein purpura, or Alport's disease, were not used as controls. Only patients with nephrotic disorders in which prednisone has been shown to be of therapeutic value[8,18] were examined. Most patients had normal serum creatinine levels. Moreover, since patients were of similar age, changes in height and height velocity could be compared. Finally, edema and hypoproteinemia was found in six group 1 and seven group 2 patients and lasted longer in the nonprednisone-treated patients.

Our findings are in contrast with the results of Sheagren et al,[10] who found no influence of alternate-day corticosteroid administration on growth potential or the tendency toward osteoporosis in rabbits. That study was performed in healthy young rabbits given methylprednisolone sodium succinate intramuscularly in a highly controlled environment and employed a single weight-based dose and route schedule. We examined patients with different glomerular diseases, treated with varying oral

doses of prednisone, who occasionally were placed on a daily dosage schedule as relapses and edema occurred. Some patients maintained on lower alternate-day prednisone doses had normal BMC/BW ratios and tended to be taller than patients receiving higher prednisone doses.

A major limitation of photon absorptiometry is that it can only detect osteopenia, but not distinguish osteoporosis from osteomalacia. However, it is plausible to assume that corticosteroid-treated patients with decreased BMC and BMC/BW ratios have the entity designated as corticosteroid-induced osteopenia, which by histologic examination appears to be predominately osteoporosis.[19] Corticosteroid-induced osteopenia results from the stimulation of bone resorption through corticosteroid-induced inhibition of intestinal calcium transport.[20,21] The influence of this reduced gut uptake of calcium in promoting increased secretion of parathyroid hormone,[22] and the direct influence of corticosteroids on vitamin D metabolism, are of less certain importance in the pathogenesis of corticosteroid-induced osteopenia found in animal studies.[23,24] Nonetheless, the finding of significant demineralization in 72% of group 1 patients and in none of the group 2 patients suggests that even an alternate-day dosage schedule can result in appreciable pathologic changes in bone.

It is well known that daily prednisone administration will result in growth retardation in addition to osteopenia. We have previously shown that patients changing from an alternate-day to a daily dosage schedule demonstrated greater demineralization after initiation of the daily dosage schedule and relative remineralization after returning to an alternate-day schedule.[5] We have further shown in this study that cessation of prednisone therapy results in increased BMC/BW ratio and augmented height. Hence, patients with glomerular disease treated with prednisone do not grow as well as patients with similar diseases not receiving corticosteroids.

An interrelationship between increased BMC and BMC/BW ratio and increased growth velocity is found in group 2 patients ($r = .77$, $P < .001$). An increase in BMC/BW is also correlated with an increase in height toward normal. No such correlation was found in prednisone-treated subjects. However, the highest prednisone dose (> 1.5 mg/kg/48 hr) is associated with the shortest heights.

Recent studies of the use of alternate-day prednisone therapy in the nephrotic syndrome have stated that this therapeutic schedule provides suppression of disease activity with minimal bone demineralization and growth suppression.[8,18] This present study suggests that prednisone therapy even in an alternate-day form may be associated with appreciable growth suppression and osteopenia. Although the development of edema and the nutritional impairment associated with disease relapse may contribute to decreased growth and demineralization, the underlying disease per se does not appear to influence these variables, as edematous patients not treated with corticosteroids did not experience a decline in BMC, height, or height velocity. Growth and the mineral content of bone are more likely influenced by the use of alternate-day glucocorticoid therapy (or daily therapy) rather than by the nature of the glomerular disease.

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A Pyridoxine-Dependent Behavioral Disorder Unmasked by Isoniazid

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• **A 3-year-old girl had behavioral deterioration, with hyperkinesis, irritability, and sleeping difficulties after the therapeutic administration of isoniazid. The administration of pharmacologic doses of pyridoxine hydrochloride led to a disappearance of symptoms. After discontinuing isoniazid therapy a similar pattern of behavior was noted that was controlled by pyridoxine. A placebo had no effect, but niacinamide was as effective as pyridoxine. Periodic withdrawal of pyridoxine was associated with return of the hyperkinesis. The level of pyridoxal in the blood was normal during the periods of relapse. Metabolic studies suggested a block in the kynurenine pathway of tryptophan metabolism. The patient has been followed for six years and has required pharmacologic doses of pyridoxine to control her behavior.**

(*Am J Dis Child* 132:773-776, 1978)

Recently, interest has been shown in using pharmacologic dosages of vitamins for treating metabolic disorders, principally the various aminoacidopathies.[1] In addition, orthomolecular psychiatric literature has advocated large doses of vitamins for treating emotional disorders, including schizophrenia.[2] Much of this literature contains little biochemical data and relies heavily on a subjective appraisal of the treatment.[3]

We report the case of a young child with hyperkinetic behavior that was accentuated by isoniazid therapy. This fortuitous observation led to the control of her behavior disorder with massive doses of pyridoxine hydrochloride. Her condition appears to differ from the well-known pyridoxine deficiencies and dependencies described in the literature.[4]

REPORT OF A CASE

The patient was the third child of nonconsanguinous parents. She was delivered on Jan 15, 1968, of a mother who had an unremarkable labor. Notable in the family history was the presence of multiple allergies to inhalants and ingestants: the mother had a milk allergy, the father an allergy to dust, and the oldest brother a milk allergy. This brother's condition was diagnosed roentgenographically as ileojejunitis that was treated with salicylazosulfapyridine (Azulfidine); his condition subsequently improved while he received a milk-restrictive diet alone. The second brother had a milk allergy associated with lactose intolerance. The maternal family history included diabetes mellitus and renal malformations. On the paternal side, one cousin died of ulcerative colitis and nephritis, and a second cousin's condition was diagnosed as schizophrenia.

A soy-based formula was substituted for a cow's milk-based formula because of diarrhea that occurred in the first month of life. At 11 months of age, the patient was placed on a gluten and milk-free diet because of chronic rhinitis and intermittent episodes of irritability associated with the introduction of solid foods. This diet eliminated much of her irritability and fussiness. The diet was discontinued in her second year of life. However, following dietary indiscretions, loose bowel movements containing mucus were noted. Several urinary tract infections occurred at 2 years of age, accompanied by fever, dysuria, irritability, fussiness, and hyperactivity. Treatment with sulfisoxazole acetyl (Gantrisin) cleared the *Escherichia coli* infection, but the irritability continued, accentuated by hostile outbursts, screaming, and temper tantrums. Urologic evaluation revealed urethral stenosis and a double ureter on the right side.

Due to persistent abdominal pains, the patient was admitted to the Sinai Hospital in Baltimore on Dec 21, 1970, for further evaluation of her condition. Findings relevant to that admission included a normal small-bowel study without evidence of regional enteritis. An intermediate PPD skin test was positive. Abdominal roentgenograms showed the presence of a small, dense, triangular shadow in the right hemiabdomen, which at laparotomy proved to be a knife blade tip, located in the vermiform appendix. A biopsy specimen of the ileum showed minimal edema of the submucosa with inflammation, but not of sufficient magnitude to be diagnosed as celiac disease. Abdominal pain disappeared following removal of the foreign body

Because of the positive tuberculin skin

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Urinary Tryptophan Metabolites* With and Without Tryptophan Loading, Before and After Pyridoxine or Niacinamide

	No Treatment		Normal Values†	Receiving Pyridoxine HCl/ 400 mg/Day		Receiving Niacinamide, 400 mg/Day	
	No Load	Tryptophan Load Test	Tryptophan Load	No Load	Tryptophan Load Test	No Load	Tryptophan Load Test
Indican	1.67	0.33	NA‡	0.61	2.41	1.56	1.47
Kynurenic acid	28.3	1[illegible].6	7.1(3.4-2)	4.34	10.4	8.25	30.1
Xanthurenic acid	4.01	5.[illegible]1	1.9(0.8-5.6)	ND‡	0.98	0.43	23.0
Tryptophan	0.15	0.52	NA	ND	2.65	1.29	4.48
Indole-3-acetic acid	0.46	0.46	NA	0.13	1.35	0.23	12.39
Kynurenine	2.43	2.74	15.6(3.8-50)	0.28	1.23	ND	22.4
3-HO-Kynurenine	1.97	C.E0	3.0(0.5-9.2)	0.76	ND	ND	ND
3-HO-Anthranilic acid	0.57	C.77	3.0(1.2-4.9)	ND	3.38	ND	3.10
N'-methylnicotinamide	1.09	0.33	0.28(0.12-0.44)	0.20	1.41	77.8	84.5
5-hydroxyindoleacetic acid	0.76	0.36	0.35(0.11-0.)	0.03	0.64	0.15	0.49
Anthranilic acid	ND	ND	NA	ND	ND	ND	10.4

*All values are expressed as μmoles kg/7 hr.
†Normal values as in O'Brien et al.[6]
‡NA indicates not available; ND, not detectable.

test, the patient was treated with isoniazid, 10 mg/kg/day. Within a week, insomnia, irritability, hyperkinesis, and temper tantrums developed. She neither listened to her parents nor allowed them to discipline her. She complained when clothing contacted her body. Results of a physical examination were normal, as was the EEG. After it had been ascertained that no new foods had been added to the diet, the possibility of isoniazid interference with pyridoxine metabolism was suspected. The administration of pyridoxine hydrochloride, 100 mg/day promptly reduced her irritability. However, it was necessary to increase the dosage to 400 mg/day to completely control all of her symptoms. While receiving isoniazid and pyridoxine, it was noted that the administration of sulfisoxazole or a decongestant syrup containing phenylpropanolamine hydrochloride, phenaramine maleate, and pyrilamine maleate (Triaminic) was also associated with the behavioral deterioration. During these periods of time, the dosage of pyridoxine was increased to 800 mg/day, and a decrease in symptoms was observed. Both isoniazid and pyridoxine therapies were discontined after six months.

After three asymptomatic weeks, behavioral problems returned. The patient again was irritable, fretful and cried. She refused to put on her clothes, particularly her shoes, complaining that her feet hurt and burned. The mother described her daughter as being wild, easily distracted, and disruptive. The patient would awaken in the middle of the night from nightmares; there was morning anorexia and loud noises would upset her. Since the symptoms were similar to those manifested while receiving isoniazid, pyridoxine therapy was again prescribed. A great improvement was noted several days later. A dosage of 400 mg of pyridoxine per day was needed to successfully control the neuropsychiatric symptoms. Again, administration of sulfisoxazole or decongestant was associated with the return of the symptoms within a week and required doubling the dose of pyridoxine for control.

Because pyridoxine is essential in the kynurenine pathway of tryptophan metabolism which results in the formation of niacin,[1] and since isoniazid therapy has been known to precipitate the symptoms of pellagra,[5] a therapeutic trial of niacinamide, 400 mg daily, was initiated. The patient responded equally well and was given niacinamide for six weeks. Subsequently, niacinamide therapy was discontinued, and pyridoxine therapy was reintroduced. During a six-year follow-up, the patient has remained asymptomatic while receiving dosages of pyridoxine hydrochloride ranging from 300 to 400/mg per day. Periodic cessation of vitamin therapy or substitution of a placebo (containing gluten-free flour) was accompanied by a rapid return of irritability, hyperactivity, hostility, aggression, paresthesis, and skin itching which developed within two weeks. However, after receiving continuous therapy for periods of six months or longer, the patient would remain asymptomatic for as long as one or two months of time after terminating vitamin treatment. When dosage exceeded 800 mg/day, headache was noted as a side effect.

During this period of time, the patient grew and developed normally, and she has achieved satisfactory grades in school. Psychotherapy has not been given. Behavioral modification techniques have been found to be ineffective during symptomatic, vitamin-free intervals.

One brother has had episodes of irritability and hyperkinesis during periods of stress or infection. The mother has given him 300 to 400 mg of pyridoxine hydrochloride daily and reported that he is asymptomatic. No placebo control or biochemical tests have been performed on the brother. The father, described as a tense individual, had been seen for psychotherapy. When the patient was 7 years old, her parents were divorced. During this period of time, her need for medication appeared to be independent of any familial stresses.

Biochemical Investigations

To elicit the etiology of the metabolic problem, we performed a series of tryptophan tolerance tests on the child at 5 years of age. L-tryptophan, at a dose of 100 mg/kg, was administered early in the morning; the metabolites of the kynurenine pathway and other tryptophan-derived products in a seven-hour urine specimen were measured. The tryptophan tolerance tests were performed while the patient was untreated and symptomatic, then after a period of four weeks while receiving pyridoxine, and finally after a period of four weeks while receiving niacinamide. Normal values after tryptophan load, as reported by O'Brien et al[6] were used for the basis of comparison. In addition, assays were done for tryptophan in the urine,[7] 5-hydroxyindoleacetic acid,[8] indican,[9] indole-3-acetic acid,[10] and *N*'-methylnicotinamide.[11] Tryptophan[12] and the level of indole in plasma in alkaline chloroform-extracted samples,[13] were also determined.

The results are given in the Table. The baseline no-load values of kynurenic and

xanthurenic acids were elevated, in amounts usually seen after tryptophan loading. This suggested a deficiency in the pyridoxine-dependent enzymes for the metabolic steps beyond these two intermediates. Increased amounts were also present during the tryptophan loading. When the patient was given pyridoxine, the amount of tryptophan and the tryptophan metabolites excreted decreased. This suggested increased metabolic activity along the kynurenine pathway due to activation of pyridoxine-dependent enzymes. After tryptophan loading, xanthurenic acid excretion was reduced, compared with the no-treatment baseline, which again indicated increased activity of the pyridoxine-dependent enzymes. The baseline elevation in N^1-methylnicotinamide was suggestive of exogenous, nontryptophan-derived niacin. Its presence contradicts the likelihood that her symptoms were due to a pellagra-like condition. The excretion of 5-hydroxyindoleacetic acid was normal in every test. However, this does not exclude an abnormality in the serotonin pathway for which pyridoxine is necessary. Coleman[14] found that 88% of hyperkinetic children had low levels of serotonin in their blood. In contrast, the patients she tested had normal amounts of 5-hydroxyindoleacetic acid in 24-hour urine specimens.

High doses of niacin normalized the baseline levels of tryptophan metabolites. However, under the stress of a tryptophan load, substantial increases occurred in all metabolites. As expected, N^1-methylnicotinamide excretion was substantially greater during niacin therapy since this compound represents the metabolic end product of that vitamin.

The fasting level of tryptophan in the plasma prior to treatment was normal, 1.47 mg/dl, as compared with a similar age control level of 1.44 mg/dl. The level of indole in the plasma was 1.37 nmoles/ml, as compared with a control value of 0.61 nmoles/ml. However, this finding cannot be offered in support of a diagnosis of tryptophan malabsorption since the urinary excretion of other direct derivatives, such as indole-3-acetic acid and indican were not increased.

To assess the role of genetic factors in the triggering effect of isoniazid therapy, an isoniazid tolerance test was performed on the patient and her mother. Both subjects were found to be slow acetylators of isoniazid. Six hours after a single dose of isoniazid, 10 mg/kg, the level of isoniazid in the mother's blood was 7.5 μg/ml; the level of isoniazid in the child's blood was 10.9 μg/ml. Under the conditions of the test, fast acetylators are those with residual levels less than 1 μg/ml, "intermediate" levels ranged between 1.0 and 5.8 μg/ml, and slow acetylators had concentrations greater than the latter value.[15]

During one hyperkinetic period when the child received only a placebo, the blood pyridoxal phosphate level was found to be normal, 11 ng/ml (normal range, 3.6 to 18.0 ng/ml as established in healthy volunteers by Bioscience Labs, Van Nuys, Calif).

COMMENT

The incidence of untoward side effects from isoniazid is dose related. At a regimen of 3 mg/kg, 1% of the patients experience side effects; when the dosage is increased to 6 mg/kg, the incidence rises to 18%. Peripheral neuritis is the most common side effect, but hepatitis, rashes, vasculitis, and arthritis may also occur. Other neurotoxic manifestations, including convulsions, transient impairment of memory, and even florid psychoses have been reported.[16,17] The psychoses are more common in patients with an unstable personality and in those with organic brain disease. Pyridoxine therapy is known to prevent the usual neurological symptoms caused by isoniazid therapy.[18]

Pyridoxine acts as a coenzyme in 60 different biochemical reactions. The recommended daily allowance of pyridoxine for children is 0.5 to 1.2 mg; for adults, 2 mg.[19] In 1953, an epidemic of infantile seizures was traced to the use of a milk-based formula unusually low in pyridoxine.[20] The role of pharmacologic doses of this vitamin as a therapeutic agent in several genetic diseases has only slowly come into focus. Six inherited disorders are known to demonstrate "responsiveness" to pyridoxine, in which patients may require 50 times, or more, the physiological dose of pyridoxine.[1,21] Our patient's clinical makeup corresponded to none of the following conditions: infantile convulsions, pyridoxine-responsive anemia, homocystinuria, cystathioninuria, hyperoxaluria, or xanthurenicaciduria. The responsiveness of the patient may consist of biochemical improvement, or in the instance of the first four diseases, symptomatic improvement may occur. Scriver[1] has attempted to discriminate between "dependency" and "deficiency" based on the concentrations of the active form of pyridoxine, and pyridoxal-5-phosphate in tissues. This differentiation is often impossible.

Although it is known that individuals with celiac disease can have malabsorption of pyridoxine,[22] the patient's overall good nutritional status, normal serum pyridoxine level, and normal ileal biopsy make this unlikely.

Large doses of pyridoxine have been used to treat behavioral disorders. Pfeiffer et al[23] have described a group of schizophrenic patients who responded to large doses of pyridoxine and zinc, with remissions of psychoses. A pyrrole, kryptopyrrole, or "mauve factor" is excreted in the urine of these persons. It theorized that the pyrrole combines chemically with pyridoxine and zinc, causing a combined deficiency.

Low levels of hydroxyindoles and serotonin have been found in the blood of hyperactive children.[14,24] Pyridoxal phosphate serves as the coenzyme for hydroxytryptophan decarboxylase, which is necessary in the final step of the synthesis of serotonin from L-tryptophan. Bhagavan et al[25] administered pyridoxine to hyperactive children, and found that the level of serotonin increased to normal and that the hyperkinesis disappeared.

Serotonin is necessary for rapid eye movement sleep.[26] When symptomatic, our patient had insomnia and nightmares. Although urinary indolacetic acid was measured, unfortunately, serotonin in the blood, was not. It might be speculated that diminished serotonin in the CNS caused the sleep disturbance.

The true incidence of children with a similar biochemically determined behavioral disorder is uncertain. Since other persons with "unstable personalities" have been described,[17] in whom psychoses developed while taking isoniazid, it would be logical to assume that additional patients with this disorder exist.

After almost seven years of therapy, the patient became unresponsive to pyridoxine. The addition of oral zinc had no effect, but thiamin, 100 mg/day, with pyridoxine reversed the hyperactivity. Pharmacologic doses of pyridoxine should be used with caution. Pyridoxine may cause deficiencies in other nutrients in the body. It

may cause a substantial drop in the level of the serum zinc and may exacerbate behavioral symptoms in some patients, particularly those with a thiamin deficiency or dependency.[27]

Pinar Ozand, MD, performed the Isoniazid tolerance test; Marvin Cornblath, MD, assisted with the preparation of this manuscript.

Nonproprietary Name and Trademark of Drug

Salicylazosulfapyridine—*Azulfidine.*

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CORRECTION

Incorrect Sentence Structure.—In the article titled "Lymphadenopathy: A Diagnostic Enigma", published in the April JOURNAL (132:353-354, 1978), the second sentence in the fifth paragraph (p 353) should read as follows: It is well to remember that generalized lymphadenopathy often results from a malignant process, bilateral lymphadenopathy, especially in the cervical area, is most likely due to tonsillopharyngitis or early infectious mononucleosis, and regional lymphadenopathy is usually a response to a focus of infection.

In addition, the first sentence of the ninth paragraph (p 354) should read as follows: This and subsequent experience reminds me of the old cliché, "One finds in a workup what one looks for." This may or may not be true.

Hyperglycinuria and Hyperglycinemia in Two Siblings With Mild Developmental Delays

Dianne Murphy Frazier, PhD; George K. Summer, MD; Harrie R. Chamberlin, MD

• **Two preschool-age siblings with similar histories of encephalopathy were examined for developmental retardation and found to have elevated levels of urinary and blood glycine. Their inability to convert glycine into serine in the absence of elevated blood and urinary ketone levels was suggestive of a defect in the glycine-cleavage enzyme system (or serine hydroxymethyl transferase). These patients differ significantly from the majority of reported cases of nonketotic hyperglycinemia in that they did not manifest life-threatening neonatal illness, severe mental retardation, or neurological deficits. However, during an oral glycine load, alterations in the electroencephalographic pattern occurred that suggested a relationship between elevated blood glycine levels and pathological involvement of the central nervous system. The ratio of CSF-blood glycine was found to be in the range expected for nonketotic hyperglycinemia.**

(*Am J Dis Child* 132:777-781, 1978)

Nonketotic hyperglycinemia, an inborn error of metabolism, is characterized by elevated blood and urinary glycine levels, failure to thrive, muscular hypotonia, lethargy, choreoathetosis, myoclonic convulsions, and mental retardation. This disorder, like ketotic hyperglycinemia, is often life threatening early in the neonatal period. Thus far, 17 patients have been described, over half of whom died within the first few weeks of life, and others have been left with severe neurological deficits and mental retardation.[1-6]

In this report, we describe two mildly retarded siblings with elevated glycine levels in blood and urine but no ketosis. The patients had occasional choreoathetosis and, following a glycine load, had abnormal electroencephalographic patterns. On the basis of a glycine loading study, glycine-serine interconversion appeared to be impaired in both patients, suggesting a partial defect in the glycine-cleavage enzyme (or serine hydroxymethyl transferase). The level of glycine in the CSF of both patients was also elevated, a characteristic finding in hyperglycinemia of the nonketotic type. However, these patients differed considerably from classical cases of nonketotic hyperglycinemia in that their clinical course and mental and motor development were only slightly below normal. In both cases, the diagnosis of encephalitis had been made during febrile episodes in infancy. This led to the diagnostic impression of postencephalitic brain damage as the cause of the neurological deficit and mental retardation. The first indication of an underlying metabolic problem came when, in the course of a developmental examination on the younger sibling at 35 months of age, urine chromatography disclosed an abnormally elevated glycine level.

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REPORT OF CASES

Case 1.—A boy was the 3,750-gm first

child of nonconsanguineous, highly intelligent parents in their mid-20s. The pregnancy had been unremarkable, and the infant breathed, cried immediately, and showed good color at birth. During his first two years, mental and fine motor development were adjudged normal by his parents, but gross motor and speech development were considered slightly below average. He sat alone at 7 months, walked alone at 15 months, and was linking three words together by 22 months.

At 22 months of age, the patient developed otitis media and a temperature of 39.4 C. Uncontrolled choreoathetoid movements, visual difficulty, and episodes of paroxysmal screaming were also noted. He was hospitalized, and a lumbar puncture showed normal CSF protein and glucose levels and no evidence of pleocytosis. After two days, he was discharged with a tentative diagnosis of "toxic or viral encephalitis." An EEG done about six weeks later was interpreted as within normal limits for age and showed no focal or paroxysmal abnormalities.

When, at age 30 months, he was referred for physical and developmental evaluation, he was in the tenth percentile for weight, between the 25th and 50th for height, and at the 50th for head circumference. The results of his physical and neurological examinations were within normal limits. However, he appeared to stumble occasionally, and his expressive speech level seemed clearly retarded. Results of routine hematologic and urinary analyses showed no abnormalities.

Psychological testing, with both the Bayley Infant Scales and the Stanford-Binet Test, gave a mental age of 23 months. Speech and language evaluation placed his receptive language at 30 months, but expressive language at 21 to 24 months. His perceptual functioning was at about 24 months, and his fine motor development at 18 to 24 months. In general, he acted immaturely and was somewhat uncooperative during the testing procedures.

Follow-up evaluations done over the subsequent six years showed continuing developmental delays. The most recent developmental assessment, with the Wechsler Intelligence Scale for Children–Revised, indicated that he had an IQ of 76 at age 9 years and 3 months.

Case 2.—This girl, 26 months younger than her brother, patient 1, was born after a full-term pregnancy and weighed 3,295 gm. Although her early mental and motor development was considered by her parents to be within normal limits, there were some specific delays. She was slow in developing adequate head support and failed to roll over until after age 5½ months. She sat without support at 7 months, pulled to standing at 12 months, and walked alone at 15 months.

At 8 months of age, she was hospitalized after three days of fever. Her temperature returned to normal on the fourth day, but she then developed a morbilliform rash of two days' duration. There was some lethargy, irritability, and a mild dysmetria on reaching for objects. Although both CSF analyses and EEG were interpreted as normal, she was discharged after three days with a presumptive diagnosis of roseola encephalitis. She also had several bouts of otitis media in her first three years of life.

At 35 months of age, she was first referred for physical and developmental evaluation. Her development appeared to be proceeding in a manner similar to that observed in her older brother at that period. She appeared to be poorly coordinated, and did not articulate well. She was a very negative child, with frequent tantrums. Her height and weight were in the 25th percentile and head circumference in the 50th. Results of physical and neurological examinations were within normal limits, except for some impairment of both gross and fine motor activity. Routine hematologic and urinary analyses were unremarkable.

Psychological testing disclosed borderline functioning, with developmental quotient indexes of 72 and 75 on the Bayley Mental and Motor Scales, respectively. She displayed poor standing balance and her running was floppy, equivalent to that of an 18-month-old child. Her fine motor skills were at the 24-month level and were interfered with by dyskinetic rotary movements of forearms, wrists, and fingers, suggestive of early athetosis.

Follow-up evaluations over the next four years continued to show developmental delay. The most recent development assessment, using the Stanford-Binet Scales, gave her an IQ of 67 at age 7 years and 2 months.

METHODS

Analyses for Amino Acids and Their Derivatives

High-voltage thin-layer electrophoresis was carried out for amino acids in urine by the method of Newton and Summer.[7] Quantitative amino acid analyses[8] of urine, deproteinized serum, and cerebrospinal fluid were carried out by ion exchange column chromatography.

During the loading studies and initial phases of dietary treatment, blood samples were taken by finger prick on filter paper and analyzed for glycine by the automated microfluorometric assay of Frazier and Summer.[9]

Urine samples were further analyzed for creatinine,[10] ketones, and methylmalonic and propionic acid content.[11]

Samples were taken only after informed consent had been obtained from the patients' parents.

Fig 1.—High-voltage thin-layer electrophoresis of 24-hour urine samples from patients, their parents, and normal control.

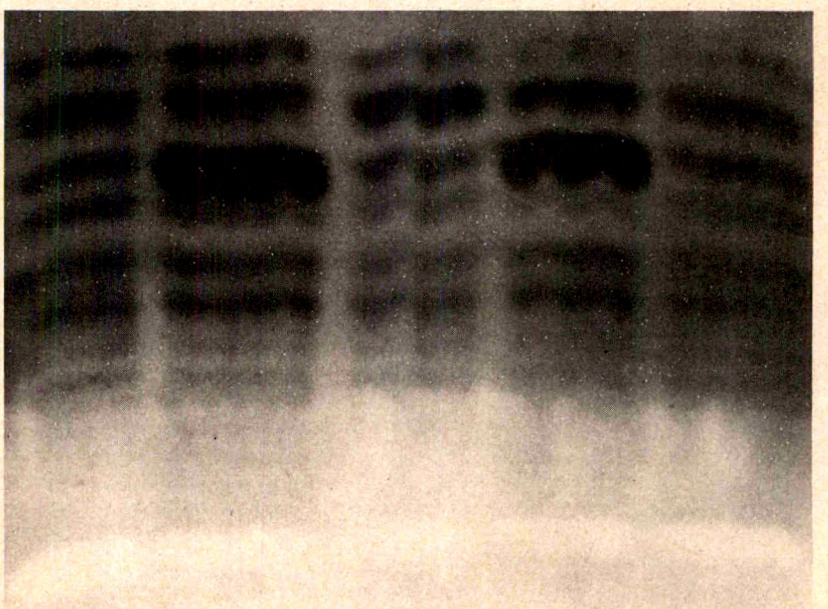


Table 1.—Glycine Concentrations in Blood and Urine

	Serum, mg/ 100 ml	Urine, μg/mg of Creatinine
Patient 1 (7 yr)	4.8	2,135
Patient 2 (4 yr)	4.5	3,082
Mother	2.7	206
Father	2.9	211
Normal	1.47-2.83	104-282
Hyperglycinemic patients	3.6-10.8	10 times normal

Glycine Loading Study

The glycine loading study was carried out over a two-day period on the patients and their parents. A 24-hour urine specimen was collected prior to oral administration of glycine. An EEG was done and fasting blood samples were taken. On the second day, each subject was given 200 ml of orange juice containing an amount of glycine equivalent to 150 mg/kg of body weight. Blood samples were taken immediately following glycine ingestion and at 45 minutes and four hours after the oral load.

Electroencephalographic Analyses

On both control and test days, an EEG was done, using a monopolar and bipolar eight-channel unit, with tracings taken while the patients were awake and asleep. The electroencephalographic recording taken during the glycine load was timed to coincide with the highest concentration of circulating glycine. The waking portions of the tracings were used for comparison.

Dietary Formulation

A relatively low-glycine diet was instituted by lowering protein intake to approximately 1.5 gm/kg of body weight per day. This decreased the daily glycine intake from approximately 3 and 4 gm to 1 and 1.35 gm for patients 1 and 2, respectively. Meal planning was carried out by the mother, with the aid of several typical meal plans and a nutritional guide that listed the protein content of all common and commercially available foods.[12] Blood samples were sent to the laboratory each week over a two-month period for glycine analysis.

RESULTS

These patients were referred for metabolic studies not because they were severely ill, but because the developmental retardation first observed in the older sibling, and initially thought to be caused by early childhood encephalitis, was being mirrored by the younger sibling. The first indication of an underlying aminoacidopathy in these patients was excessive urinary glycine detected by high-voltage thin-layer electrophoresis (Fig 1) and an elevated blood glycine level determined by the automated fluorometric method developed in our laboratory. As there was no indication, by the former method, of a generalized aminoaciduria, and since the glycine tubular reabsorption rates, calculated by the method of Scriver and Davis[13] were well above 90%, the hyperglycinuria did not appear to be of renal origin. Ion-exchange chromatography of serum and urine from both siblings showed the concentration of glycine to be in the range reported for confirmed cases of hyperglycinemia (of either the ketotic or nonketotic type), while serum and urinary glycine levels in the parents were in the high normal range (Table 1). No abnormalities of other amino acids were found in either serum or urine.

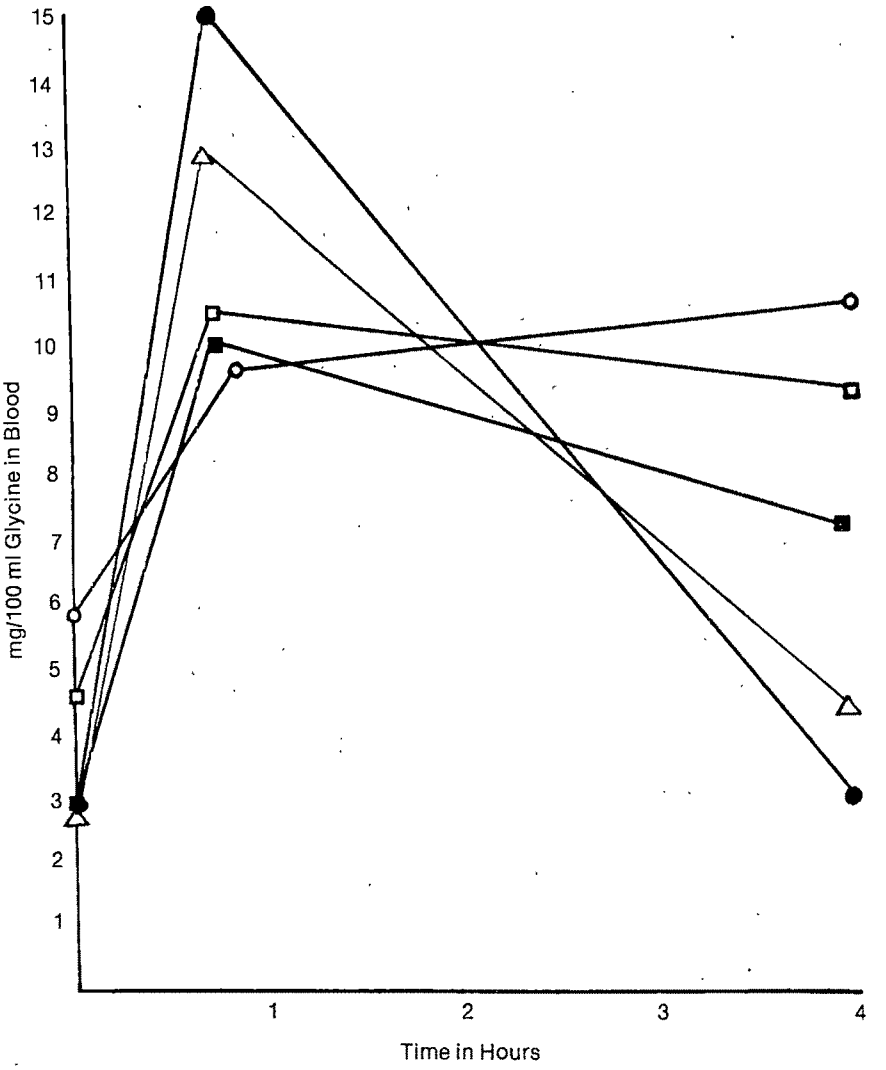


Fig 2.—Glycine levels in venous blood after glycine load of 150 mg/kg of body weight for suspected nonketotic hyperglycinemic patients 1 (open circle) and 2 (open square), their parents (solid circle and square), and normal control (open triangle).

An oral glycine tolerance test (150 mg/kg) confirmed an abnormality in glycine metabolism in both siblings. As can be seen in Fig 2, patients 1 and 2 had maximal blood glycine levels of 9.6 and 10.5 mg/100 ml, respectively, and the concentrations remained substantially elevated as long as four hours after the oral load. Normal individuals usually demonstrate a return

Table 2.—Urinary Serine and Glycine Levels (mg/24 hr) Before and After Oral Glycine Load

	Before*		After†	
	Glycine	Serine	Glycine	Serine
Patient 1	442	16	1,116	16
Patient 2	550	22	1,189	25
Mother	133	25	598	54
Father	139	25	485	66
Control	120	54	446	76
Control	112	43	463	89

*The 24-hour period immediately prior to oral glycine ingestion.
†The 24-hour period immediately following oral glycine ingestion.

Table 3.—Cerebrospinal Fluid Glycine Concentrations

Sample	Glycine, μmoles/Liter
Patient 1	41.9
Patient 2	51.8
Controls* (N = 3)	5.4-6.5
Nonketotic hyperglycinemia[24]	98
Ketotic hyperglycinemia[24]	11
Ketotic hyperglycinemia[21]	5.5
Nonketotic hyperglycinemia[21]	159
Nonketotic hyperglycinemia[21]	142
Nonketotic hyperglycinemia[21]	87
Controls[21] (N = 34)	5.2-6.6

*Samples from hospital patients tested for encephalitis and shown to be normal.

to baseline blood glycine levels within that time.[6,14] The profile of the father's blood glycine concentration during the load appeared to be similar to the profile of the normal control, whereas the mother's response was midway between that of the normal control and that of the patients. The results are similar to those reported by Ando and Nyhan[15] for obligate heterozygotes of nonketotic hyperglycinemia.

Electroencephalographic studies done on hyperglycinemic patients have shown abnormalities described by most investigators as hypsarrhythmia.[16] The preload, or control, EEGs for our patients were normal; however, when the glycine level in the blood was at its peak, the EEGs showed a consistent slowing of the theta waves in both children. No alteration in the electroencephalographic patterns of the parents was induced by the glycine load.

We attempted to lower the serum glycine levels by decreasing glycine intake. It was determined that the patients, prior to initiation of therapy, were consuming two to three times the minimum daily requirement of protein for their size and age. Restrictions of glycine were imposed by decreasing protein intake to approximately the minimum daily requirement—1.5 gm/kg of body weight per day.[17] The lowering of dietary glycine in other cases of hyperglycinemia has been ineffective in reversing neurological abnormalities[18,19]; however, similar low-protein diets have been effective in alleviating some of the behavioral problems associated with other aminoacidopathies.[20] Within five weeks of the initiation of the diet, in which glycine intake was approximately one third of the prediet intake, the patients' blood glycine levels dropped to within normal limits. The patients remained on the restricted diet for more than a year. Although there were no improvements in developmental indexes, it was believed that the lowered diet, combined with a program of behavioral modification, was effective in reducing tantrums and negative behavior.

There are several enzymatic defects that can result in an elevated concentration of glycine in the blood. There are at least four primary defects known to cause the ketotic form of hyperglycinemia.[21] Although neither sibling had a history of ketotic episodes, Baumgartner et al[22] has recently stated that the milder cases of the so-called ketotic form may not always show evidence of clinical ketosis. We therefore looked for the organic acids expected to be present in the urine should the hyperglycinemia be the result of one of the ketotic disorders: methylmalonic aciduria, propionic acidemia, or isovaleric acidemia. Gas chromatographic analysis showed no abnormal elevations of the organic acids that are indicative of these respective disorders. The nonketotic form of hyperglycinemia is believed to be due to a defect in the glycine-cleavage enzyme, which catalyzes reaction (1) of the following sequence:

$$\begin{array}{l} CH_2NH_2 + NAD + FH_4 + H_2O \rightarrow \\ | \\ CO_2H \\ \text{glycine} \end{array}$$

$$CO_2 + NH_3 + NADH + FH_4CH_2OH \quad (1$$

$$\begin{array}{l} CH_2NH_2 + FH_4CH_2OH + NAD \rightarrow \\ | \\ CO_2H \\ \text{glycine} \end{array}$$

$$\begin{array}{l} CH_2OH + FH_4 + NADH \qquad (2) \\ | \\ CHNH_2 \\ | \\ CO_2H \\ \text{serine} \end{array}$$

FH_4 and FH_4CH_2OH represent tetrahydrofolic and hydroxymethyltetrahydrofolic acid, respectively. Using carbon 14-labeled 1-glycine and 2-glycine, several investigators[16,23] have reported equal incorporation rates of the labeled carbon into serine in patients with nonketotic hyperglycinemia resulting from deficiency of the glycine-cleavage enzyme. Such a defect would also be reflected by unchanged serine levels in the blood or urine with increased glycine intake.[16] Glycine and serine levels were analyzed in the urine before and after the glycine load in all members of our family. The concentration of urinary serine for patients 1 and 2 was essentially unchanged at the highest serum glycine levels (Table 2). The parents, on the other hand, showed increases in urinary serine concentration following the oral load, although their preload serine values were not as high as those of the controls. The lack of conversion of glycine to serine in patients 1 and 2 supports the hypothesis that a defect in the glycine-cleavage enzyme may explain the nonketotic hyperglycinemic condition in these patients. Similar lack of conversion of glycine to serine was seen in a patient described by Larbre et al[14] in 1970.

COMMENT

Recent work of Perry and colleagues[21] has shown that nonketotic hyperglycinemia, unlike other hyperglycinemias, is characterized by a marked accumulation of glycine in the brain. We therefore measured the glycine concentrations in the cerebrospinal fluid of our two patients. As shown in Table 3, patients 1 and 2, with CSF glycine concentrations of 41.9 and 51.8 μmoles/100 ml, respectively, have levels significantly above those in either normal controls or patients with the ketotic form. The fact that the values for our patients were not as high as those reported by Perry et al may be due to the fact that our patients were receiving a low-protein diet at the time the samples were taken. Also, it should be noted that some of Perry and colleagues' samples, in contrast to ours, were taken at autopsy. Levy et al,[24] however, have stated that more important than the absolute CSF glycine concentrations in determining the effect of glycine on the central nervous system is the ratio of CSF to blood glycine concentration. Ratios of 8.25 and 6.25 for patients 1 and 2, respectively, are more in line with the range of ratios from 3.03 to 14.5 obtained by Levy et al[24] and by Perry et al[21] for other nonketotic hyperglycinemic patients.

Thus far, most cases of either ketotic or nonketotic hyperglycinemia described in the literature have been either severely ill neonates or profoundly retarded older patients. A mildly affected ketotic patient has been reported[14] who showed clumsiness, slight developmental retardation, and a response to glycine loading similar to that in the two nonketotic patients described in this report. Among cases of nonketotic hyperglycinemia, we are aware of four with less severe neurologic involvement than all cases thus far fully reported. One was briefly reported by Levy et al[24] in an abstract; the other three are unpublished (W. L. Nyhan, oral communication, Jan 16, 1976). Yet it appears that all four of these patients, though less severely neurologically involved than is typical, were more retarded than the two siblings reported here.

The evidence presented suggests that our patients probably have a form of nonketotic hyperglycinemia due to a variant form of the glycine-cleavage enzyme, which has partial activity. The initial manifestations of central nervous system involvement in these two patients should alert clinicians to the possibility of occurrence of similar cases of mild to moderate severity where transient neurological symptomatology associated with febrile illness might wrongly be attributed to mild encephalitis or other forms of encephalopathy. Appropriate biochemical tests are indicated under these circumstances to exclude a possible underlying metabolic disorder.

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Diagnostic Value of the Muscle Biopsy in the Neonatal Period

Harvey B. Sarnat, MD

• **Muscle biopsy specimens of 20 full-term neonates (13 surgical and seven necropsy specimens) with clinical evidence of neuromuscular disease were studied to determine the diagnostic usefulness of this procedure in the newborn. Characteristic pathologic alterations were identified in specific diseases. Some findings were similar to those seen later in life, but others differed from those expected in the same diseases at older ages. Persistence of fetal muscle cells was a characteristic common to several congenital myopathies and neuropathies. Lymphocytic infiltrates, muscle fiber necrosis, and architectural alterations of the muscle fibers were not seen at birth. Extramedullary hematopoiesis may involve newborn muscle. Muscle biopsy is a safe and simple procedure in the neonatal period and has a diagnostic reliability as good as at older ages, but histochemistry and sometimes electron microscopy are essential supplements to classical histology for interpretation. Recommended indications for muscle biopsy in the neonatal period are multiple joint contractures at birth or hypotonia and weakness, of unknown origin.**

(*Am J Dis Child* 132:782-785, 1978)

Clinical signs of neuromuscular disease often may be recognized in the neonatal period. A means of early, accurate diagnosis would not only provide a basis for prognosis and genetic counseling, it would also affect the medical and orthopedic management of the affected neonate. The clinical usefulness of the muscle biopsy in the neonatal period depends on careful selection of patients, the application of modern laboratory techniques such as histochemistry and electron microscopy to supplement classical histology, and the recognition of reliable criteria of normal and pathologic states of striated muscle at birth. In some diseases, the pathologic findings in the neonatal period resemble those found at older ages; in others, the findings differ considerably from those expected later in life.

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Read before the annual meeting of the Australian Association of Neurologists, Melbourne, March 23-25, 1977.

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METHODS

Open biopsies of the gastrocnemius or quadriceps femoris muscles were performed in 20 full-term infants over a three-year period in the neonatal nurseries of Cardinal Glennon Memorial Hospital for Children, St Louis, and Princess Margaret Hospital for Children, Perth, Australia. Thirteen were surgical biopsies and seven of the specimens were taken postmortem. Normal control muscles also were taken postmortem from six full-term neonates and six premature infants of 26 to 36 weeks' gestation, none of whom had evidence of neuromuscular disease.

Indications for surgical muscle biopsy in neonates were a suspicion of neuromuscular disease in infants with generalized hypotonia and weakness or arthrogryposis multiplex congenita. Local anesthesia with 1% lidocaine hydrochloride was used. Blood loss was negligible. Complications did not occur.

Tissue was rapidly frozen in isopentane (2-methylbutane) cooled to −160° C in liquid nitrogen. Sections of 6 or 8 μ were cut in a cryostat. Hematoxylin-eosin and modified Gomori trichrome stains were applied, and other sections were incubated for (1) the histochemical demonstration of nicotinamide adenine dinucleotide tetrazolium reductase (NADH-TR), total phosphorylase, myofibrillar adenosine triphosphatase (ATPase) preincubated at a pH of 9.4, 4.7, and 4.4, (2) the PAS reaction with diastase control, and (3) oil red O stain.

Electron microscopy was performed in selected cases.

RESULTS

Surgical biopsy specimens were interpreted as abnormal in every case except one. Specific pathologic diagnoses of surgical and postmortem muscle biopsy specimens included three cases of Werdnig-Hoffmann disease (surgical), two cases of neuropathy that were due to meningomyelocele (postmortem), one case of familial infantile polyneuropathy (surgical), one case of presumed neuropathy involving lower limbs only and in which a structural lesion of the lower spine was not demonstrated by myelography (surgical), two cases of amyoplasia associated with agenesis of lumbar and sacral vertebrae[1] (postmortem), and four cases of neonatal myotonic dystrophy, previously reported[6] (surgical and postmortem).

Other diagnoses included one case of myotubular myopathy without differentiation of histochemical fiber types (surgical), three cases of congenital muscle fiber-type disproportion that included one with internal nuclei in muscle fibers of small and large size (surgical), two cases of extensive intramuscular hematopoiesis in infants with severe erythroblastosis fetalis (postmortem), and one case with a normal neonatal muscle biopsy specimen to which the nondiagnostic term "benign congenital hypotonia" was applied because of generalized hypotonia and absent tendon reflexes. Subsequent motor development was almost normal to 1 year of age, but hypotonia and areflexia persisted without weakness, and the patient had no other neurologic deficits (surgical).

Normal muscle is mature histologically and histochemically, except for size of individual muscle fibers, by 30 weeks' gestation. The full-term neonate normally has a mosaic distribution of equal numbers of types I and II muscle fibers. The two histochemical fiber types are approximately equal in size under normal conditions and have an average cross-sectional diameter of 15 μ. Type I fibers are defined histochemically by a relatively large number of mitochondria and high concentrations of oxidative enzymes, low concentrations of glycogen and glycolytic enzymes, and a weak reaction for myosin ATPase at a high pH but a strong ATPase reaction when tissue sections are preincubated at a low pH. Type II muscle fibers have a reverse metabolic profile; oxidative enzymes are in low concentration, glycogen is abundant, glycolytic enzymes are high in concentration, and the myosin ATPase reaction is strong at a high pH and almost completely inhibited at a low pH. The differences between muscle fiber types are only quantitative and thus relative.

Diseases for Which Characteristic Histopathologic Findings Are Identified at Birth

Werdnig-Hoffmann Disease.—The well-known profile is already apparent at birth. Fascicles of rounded atrophic muscle fibers are of mixed histochemical types. Groups of hypertrophic fibers are almost exclusively of type I with ATPase stains but are of mixed type when NADH-TR, phosphorylase, and PAS stains are applied. Perimysial connective tissue is greatly increased, but endomysial collagen is usually sparse. Scattered myotubes are seen.

Denervation Other Than Werdnig-Hoffmann Disease.—Congenital neuropathies may be due to meningomyelocele, diastematomyelia, tumors or dermoics of the sacral region involving the cauda equina, infantile polyneuropathy, or a poorly defined caudal form of spinal muscular atrophy different from Werdnig-Hoffmann disease. In these conditions, the adult-type histologic pattern of scattered atrophic muscle fibers of both major histochemical types is seen, but type grouping associated with reinnervation is generally poorly developed because of the short period of pathogenesis. Giant fibers of Werdnig-Hoffmann disease are not found. A feature of denervated neonatal muscle, not found in neurogenic atrophies beginning at older ages, is the presence of scattered fetal myotubes and other immature muscle cells. Infants with lumbosacral meningomyeloceles or with sacral agenesis often have small muscles in the calves and thighs that are usually replaced by connective tissue and fat. Primary amyoplasia is postulated as an additional factor in the pathogenesis since the muscles are derived from the same embryonic mesodermal somites that give origin to the dysplastic or absent bony vertebrae.[1]

Duchenne Muscular Dystrophy.—Muscles of male fetuses of 18 to 20 weeks' gestation with high placental blood concentrations of creatine phosphokinase (CPK) already show wide variation in muscle fiber diameter, hyalinized fibers, and increased connective tissue.[2,3]

Myotonic Muscular Dystrophy.—Full-term infants with the severe neonatal form of this disease have muscle fibers that appear to be arrested or delayed in various stages of maturation. Myoblasts, myotubes, myocytes not completely differentiated histochemically, and mature muscle fibers are all seen within the same muscle.[4-6] However, the degenerative changes of adult myotonic dystrophy are not found.

Centronuclear (Myotubular) Myopathies.—Autosomal recessive congenital myopathies have been described that are characterized pathologically by muscle composed of fetal myotube-like muscle fibers.[7] Some sporadic cases may involve severe weakness resulting in respiratory distress in the neonatal period.[8] Another myopathy, transmitted as an X-linked recessive trait, may cause severe symptoms or death shortly after birth; similar histologic features of persistent myotubes are seen in the neonatal muscle.[9]

Congenital Muscle Fiber-type Disproportion.—This condition requires muscle biopsy for diagnosis. Muscle fibers of histochemical type I are uniformly smaller than those of type II although they are otherwise mature.[10] In the neonatal cases reported by Fardeau et al,[11] the average diameter of type I fibers was 12 μ. In one of our cases, the average cross-sectional diameter of 100 type I fibers was 7.5 μ (3.5 to 15 μ) and that of 100 type II fibers was 22 μ (range, 15 to 28 μ), indicating that mild compensatory hypertrophy of type II fibers had already begun. A

similar degree of disproportion was found in our other cases, both with and without central nuclei; type I fibers were hypoplastic and type II fibers were mildly hypertrophic. In older infants and children, type I muscle fibers may achieve normal size, but the disproportion persists because of uniform hypertrophy of type II muscle fibers.[10]

One of our three neonatal patients with these findings also had central nuclei in more than half of her muscle fibers of both sizes and histochemical types. A repeated biopsy specimen taken when the patient was 5 years old showed the same findings of fiber-type disproportion and central nuclei, and she had nonprogressive hypotonia and mild generalized weakness. This case probably represents a variant of congenital muscle fiber-type disproportion, but the relation to other centronuclear myopathies is uncertain. Similar cases have previously been reported in children.[12-14]

Unclassified Congenital Muscular Dystrophies.—Many sporadic cases have been reported of symptomatic congenital myopathies of early infancy characterized pathologically by specific alterations of muscle, including abnormal variation in muscle fiber diameter and proliferation of connective tissue.[15-17] Such conditions, sometimes labeled "congenital muscular dystrophy" almost certainly constitute a heterogeneous group of poorly understood diseases. Some of these cases were associated with malformations of the CNS.[18,19]

Metabolic Myopathies.—Muscle diseases having abnormal muscle mitochondria, glycogen storage diseases, lipid storage diseases of muscle, and other genetically determined metabolic myopathies may have clinical manifestations early in life. The neonatal muscle biopsy has not been sufficiently studied to determine its value in these conditions, although it offers a potential for early diagnosis.

Intramuscular Hematopoiesis.—Two infants had severe erythroblastosis fetalis that was due to Rhesus sensitization. Exchange transfusion was performed a few minutes after delivery, but the infants died within hours. At the time of necropsy, paraffin sections of multiple skeletal muscles, stained with hematoxylin-eosin, disclosed extensive cellular infiltrates of the perimysial connective tissue, especially around blood vessels. The cells also invaded the muscle fascicles focally, but no muscle fiber necrosis or myopathic alterations of muscle fibers were seen. At low magnification, the histologic appearance was that of an intense inflammatory myopathy, but higher magnification showed that the infiltrating cells were normoblasts and myelocytes. Extramedullary hematopoiesis also was found in the liver, kidneys, and other organs.

COMMENT

The results of this study and review of the literature allow the conclusion that the diagnostic capability of the muscle biopsy is as good in the neonatal period as at older ages. To achieve this capability, however, it is essential that classical histology be supplemented by modern laboratory techniques of histochemistry and sometimes electron microscopy, and that interpretation be made by a physician experienced in pediatric muscle pathology. Because muscle biopsies have been attempted only recently in the neonatal period, the procedure is still in transition from the investigative to the routine clinical diagnostic phase of development. It is now recognized, however, that if the suspicion of neuromuscular disease is high in a newborn, the procedure need not be deferred until an older age because of concern that the pathologic findings will not yet be diagnostic at birth.

The indications for muscle biopsy in the neonatal period remain a matter of clinical judgment. Family history and clinical signs often are distinctive enough to make a confident clinical diagnosis of such diseases as neonatal myotonic dystrophy and Werdnig-Hoffmann disease without confirmation by muscle biopsy. Duchenne muscular dystrophy may be diagnosed in male infants at 1 week of age by CPK determination since an elevated concentration of this enzyme already occurs in the second trimester of gestation.[2,3] (Serum CPK is mildly elevated for a few days after delivery in normal infants, but this transient elevation does not persist.) Although the muscle biopsy specimen of male infants affected with Duchenne muscular dystrophy also would be expected to be abnormal, this additional information might be redundant. Congenital myasthenia gravis is diagnosed on the basis of prostigmine test and electromyography, rather than by muscle biopsy.

Other neonates have symptoms and signs of neuromuscular disease but lack a helpful family history, and the nature of their illness is not obvious from physical examination alone. For these infants, the principal indications for neonatal muscle biopsy are the following: (1) multiple congenital contractures (arthrogryposis multiplex congenita), and (2) generalized weakness and hypotonia of unknown etiology. Tendon reflexes are nearly always diminished or lost in symptomatic neonates with generalized neuromuscular disease, and brisk knee jerks are evidence against this diagnosis.[20] Muscle bulk may be greatly decreased or replaced by subcutaneous fat but may be normal at birth in some myopathies.

The routine application of histochemical methods to clinical muscle biopsy specimens in the past two decades has permitted the discovery of many new congenital and metabolic myopathies. Some, such as the lipid myopathy that is due to muscle carnitine deficiency, are treatable by diet and specific replacement therapy. Some other identified myopathies are nonprogressive and have a relatively good prognosis. An example of the latter is congenital muscle fiber-type disproportion. This disorder is characterized at birth by hypotonia, variable weakness, and often by contractures of distal and proximal joints.[10] The diagnosis requires a muscle biopsy, which may be made at birth, as shown previously[11] and confirmed in this study. Infants with this disorder generally improve in strength, have normal intelligence, and their contractures respond to physiotherapy without need for plaster casting or surgery.[10] The management and prognosis of such cases clearly differ from those of infants with muscular dystrophy, Werdnig-Hoffmann disease, or

other progressive diseases, and early diagnosis by muscle biopsy is advantageous.

Infiltrates of blood-forming cells in muscle probably are asymptomatic and do not lead to irreversible damage or fibrosis. Inflammation, in the form of perivascular and interstitial infiltrates of lymphocytes in muscle, has not been reported for neonates. Even later in infancy, this finding generally signifies a muscular dystrophy rather than polymyositis.[20] Necrosis of muscle fibers was not found in any of our patients, even those with myotonic dystrophy, in contrast with the condition in later childhood and adult life. Muscle fiber necrosis also was not seen in fetuses at risk for Duchenne muscular dystrophy[2,3] and has not been reported in neonatal muscle in any condition except, perhaps, trauma. None of our cases or those neonates previously reported by others has shown architectural alterations of muscle fibers, such as whorls, splitting, or striated annulets.

Muscle biopsy is feasible in even the weakest infants, who need not be removed from their isolettes. Local anesthesia is satisfactory, and the risks of general anesthetics are avoided. Blood loss is negligible. Needle biopsy techniques have been developed in some centers that further simplify the surgical procedure and provide satisfactory specimens for diagnostic purposes in young infants.[21] Thus, muscle biopsy is a low-risk procedure offering the potential for diagnosis of many neuromuscular and metabolic diseases at birth.

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Kleine-Levin Syndrome Associated With Fire Setting

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• **Kleine-Levin syndrome is characterized by periodic hypersomnia associated with megaphagia and striking behavioral and psychiatric symptoms; it occurs primarily in adolescent boys. We treated a 17-year-old boy who had typical recurring somnolent episodes. His bizarre behavior included fire setting and stealing, both of which may have represented compulsions. His EEG during a sleepy episode was diffusely abnormal with generalized slowing of background activity; as he awoke and improved clinically, his EEG returned to normal. Between episodes, his EEG was normal. The relationship between Kleine-Levin syndrome and other sleep disorders is discussed. The neurochemistry and neurocircuitry that may provide the requisite substrate for this complex and fascinating neuropsychiatric disorder are briefly reviewed.**

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The Kleine-Levin syndrome is characterized by periodic hypersomnia usually associated with megaphagia; it occurs predominantly in adolescent boys. Striking behavioral symptoms may precede, follow, or coincide with the sleeping episodes; these include motor restlessness, truculence, and uninhibited sexuality. Other reported psychiatric symptoms include alterations in sensorium, amnesia, affective symptoms, delusions, and hallucinations. The sleeping episodes characteristically start suddenly, last several days, recur at intervals of several months, and cease completely by the third decade. Precipitating factors may or may not be identifiable. The typical patient is completely normal between episodes. Electroencephalographic abnormalities of a diffuse, generalized type have been reported in some cases during the episode. Treatment with cerebral stimulants, amphetamines, or methylphenidate hydrochloride may abort an episode.

This syndrome was initially delineated by Levin[1] using two cases described by Kleine[2]; it was designated the Kleine-Levin syndrome in 1942 by Critchley and Hoffman.[3] In 1962, Critchley[4] reviewed the 26 known cases, and an article by Jeffries and Lefebvre in 1973 cites 40 known cases.[5]

In the various cases reported in the literature, the primary clinical finding was periodic hypersomnolence. The disorders of excessive sleep can be divided into two main types: narcolepsy and hypersomnia. Narcolepsy is characterized by brief episodes of sudden, irresistible sleep attacks after which the patient awakes alert and refreshed. In the hypersomnias, the onset of sleep is more gradual, the sleep episode is prolonged for hours or days, the patient is difficult to arouse, and on awakening, he is drowsy, irritable, slow in mentation, and may have alterations in sensorium. Cataplexy, sleep paralysis, and hypnogogic hallucinations are typically seen in narcolepsy, but not in the hypersomnias.

The EEGs obtained during sleep have been extensively studied in narcolepsy and indicate that in those patients with cataplexy, the nocturnal sleep and the sleep attacks begin with rapid eye movement (REM) sleep. The hypersomnias have been less well studied, but include the Kleine-Levin syndrome and the Pickwickian syndrome, both of which are associated with eating disorders. The sleep EEG was rigorously studied by Billiard et al[6] in one female patient who may have had Kleine-Levin syndrome. Wilkus and Chiles[7] studied the EEGs of an adolescent boy with the typical

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findings of Kleine-Levin syndrome. During a sleeping episode, they noted diffuse abnormalities and stage REM at sleep onset during diurnal recordings; two overnight EEGs recorded during an attack did not show sleep-onset REM, although stage 3, 4, and REM sleep were decreased. The recordings were normal between episodes. Although their patient did not have the typical brief sleep attacks of narcolepsy nor any of the usually associated symptoms, the finding of REM at sleep onset blurs the EEG distinction between narcolepsy and the periodic hypersomnias.

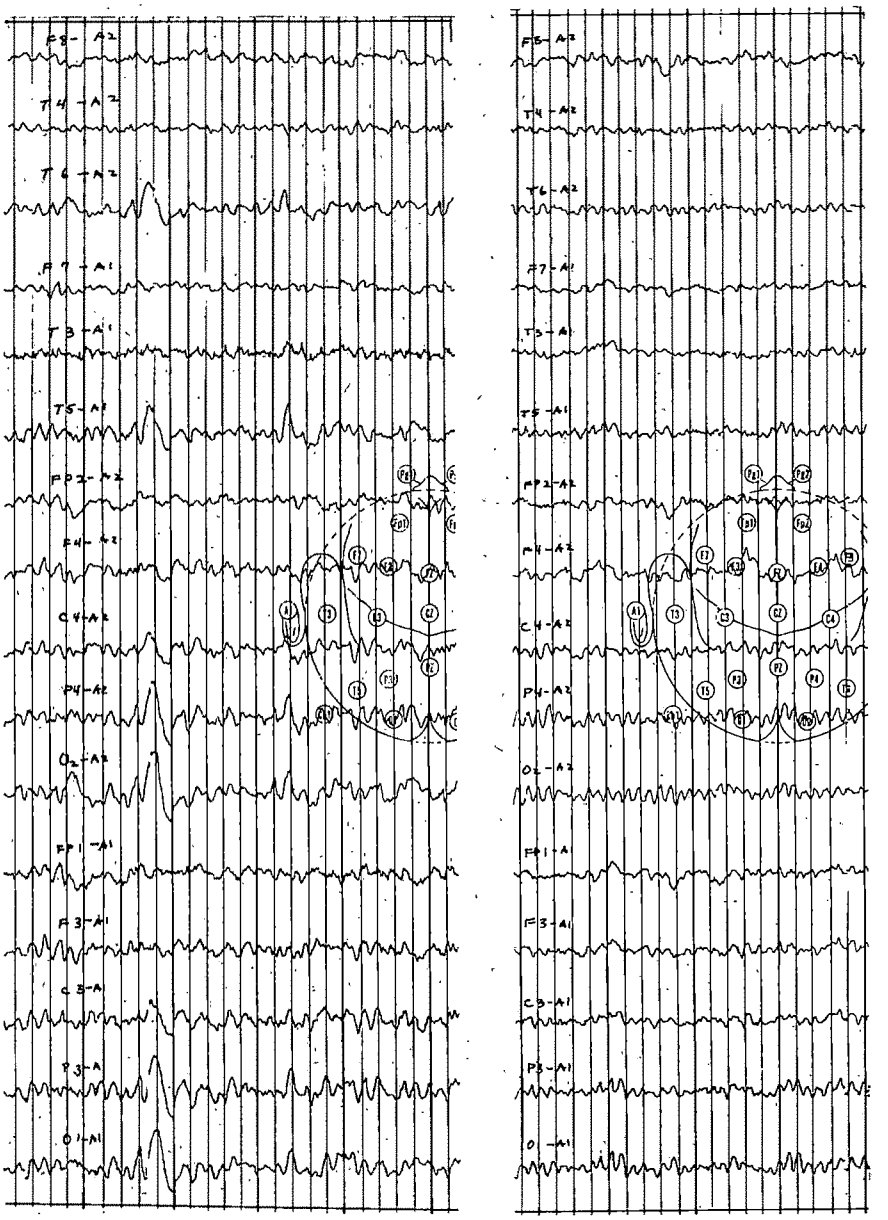
Through the centuries, man has been as fascinated by fire as he is curious about dreaming and sleeping. Mythology and folklore is replete with references to fire. Greek philosophy included elaborate theories about fire and its importance in the creation of the universe. Fire setting as a psychiatric symptom has been studied in retrospective psychodynamic case reports and in terms of phenomenology of the symptom. The various psychodynamic theories of fire setting in children and adolescents are succinctly summarized in a review by Heath et al.[8]

The freudian theory that fire setting and enuresis are related to sexual drives has greatly influenced later writings. Fenichel[9] theorized that fire setting is the expression of a sadistic drive seeking to destroy the loved object. Kaufman et al[10] viewed fire setting as an ego defense mechanism that transforms passive helplessness into active mastery. Although epidemiological studies suggest a tentative link between fire setting and enuresis[11] and between fire setting and low IQ,[12] these associations are not proved. Although fire setting, enuresis, and animal cruelty in childhood have traditionally been considered a triad predictive of later violence,[13] rigorous studies of the association between fire setting and violence are not available. Fire setting may represent a compulsion; although most children and adolescents who set fires are unable to offer explanations for this behavior, many of these youngsters do describe an irresistible urge to set and watch fires.

We studied an adolescent boy with Kleine-Levin syndrome whose behavioral disturbances included fire setting. Electroencephalograms were obtained during hypersomnic episodes, during treatment with a cerebral stimulant, and during an asymptomatic period.

REPORT OF A CASE

A 17-year-old adopted boy had problems beginning when he was 14 years of age, when he started to steal small amounts of money from his parents and was suspended from school for rowdy activities. During this time, strange sleeping behavior began, exemplified when he was found sleeping under a neighbor's porch. During an examination at the office of his pediatrician, he refused to answer questions, stared straight ahead, and when asked for a urine specimen, started for the bathroom, stopped, returned, and would not answer questions. The patient was hospitalized for bizarre behavior, lethargy, and excessive sleeping; a psychiatrist and neurologist were consulted. He was irritable and negativistic with the nurses in the hospital,



Left, Patient in somnolent period. Background activity of 5 to 6 counts per second (cps) with bursts of high-amplitude, slow-wave action appear predominantly in posterior head regions. Right, Patient in awake period. Normal background activity of 8 to 9 cps and normal record is seen.

refused food, and once tried to leave the hospital. No definitive diagnosis was made.

During the next seven months, the patient had four similar episodes. During each episode, the patient was truculent and had aggressive behavior during one of these periods of somnolence, striking his dog. On another occasion, he went through the motions of smoking a cigarette when he did not have a cigarette. During one hospitalization, he expressed several paranoid ideas and had visual and auditory hallucinations. For example, once he was afraid people were trying to kill him, and brought his razor to the nursing desk to prevent this; he also hid his thermometer so people could not steal it. These thoughts were expressed mostly at night, and all occurred during the sleepy period. The auditory hallucinations were usually threatening voices, although on one occasion, he hallucinated that his therapist was verbally reassuring him. During these sleepy periods, he had only one episode of proved megaphagia, when he suddenly ate two trays of food. Following each somnolent episode, he was amnesic for most of his unusual behavior.

During several of these somnolent episodes the EEGs were abnormal (Figure, left), showing diffuse slowing; during his interim normal periods, the EEG was found to be normal (Figure, right). During these normal periods, he seemed cheerful, relatively cooperative, and was described by his parents as "his old self."

The patient's subsequent course was one of numerous hospitalizations, several to a psychiatric ward. Several diagnoses were considered, including postencephalitis syndrome (he had chicken pox encephalitis at age nine years, with no demonstrable residual effects) and schizophrenia (made during a somnolent period when the patient had hallucinations). Twice during somnolent periods, the patient described an urge to set fires. Once he considered setting fire to drapes in the hospital, and once he lit a match to the end of a thermometer to watch the mercury rise. On the day of discharge from an early hospitalization, he went to a neighbor's house, stole some football tickets, masturbated into his mother's underwear, and set fire to his neighbor's drapes. He then called the fire department and tried to put the fire out himself. This precipitated the two-month psychiatric hospitalization, and the diagnosis of Kleine-Levin syndrome was then considered. Treatment with amphetamines was started, and he awoke. An EEG at this time was normal. The medication was stopped after three days, and since then he has had two recurrences, each of which were successfully managed with a brief course of amphetamines.

LABORATORY DATA

Laboratory results, summarized from several hospitalizations, were as follows: CBC counts were always normal; and liver enzyme levels, kidney function tests, serum electrolyte values, protein studies, and glucose concentration were all normal. Drug screens were negative. The VDRL was nonreactive. An EEG, performed with use of nasopharyngeal electrodes, failed to show temporal lobe spikes. Computerized axial tomography was normal. His IQ scores were in the normal range. Academic achievement testing showed he was one to two years behind his school level. Projective testing during a lethargic episode when the patient was having hallucinations was interpreted as showing noteworthy psychological deterioration in the form of psychosis.

COMMENT

This patient clearly meets the major criteria of Kleine-Levin syndrome. He is an adolescent boy with periodic episodes of hypersomnia that are associated with an abnormal EEG. Behavioral disturbances (eg, fire setting and animal cruelty,) or psychiatric symptoms (truculence, paranoid ideation, suicidal thoughts, and logorrhea) were present, concurrent with or immediately subsequent to the sleepy episode. Between episodes he was symptom-free, had a normal EEG, and was amnesic about most of the hypersomnolent period. He had only one proved episode of megaphagia during a sleep episode. Megaphagia, although frequent in this syndrome, may be absent. Two of the five patients reported by Kleine did not have megaphagia. Fresco et al,[14] in a series of 58 male patients, noted that megaphagia was absent in 24 (41%) of them.

Critchley initially noted that the EEGs of patients with Kleine-Levin syndrome were abnormal during the hypersomnolent period and reverted to normal between episodes.[4] Since then, there have been scattered reports of generalized abnormality during episodes. In our patient, there was generalized slowing of the background activity but no evidence of asymmetry or spike activity during the hypersomnolent periods. One of us (P.S.P.) was present during the diurnal recording when the patient was irritable (Figure), but he responded to questions with brief, appropriate answers. In this patient, no sleep-onset REM was noted, in contrast to the patient described by Wilkus and Chiles.[7] When the patient improved clinically his EEG returned to normal, and an EEG taken between episodes was normal. Twenty-four-hour polygraphic EEG recordings have been performed by Popoviciu and Corfaiu[15] in an apparently typical patient who had a massive decrease in REM sleep. Billiard et al[6] reported 24-hour recordings in a female patient, but since most patients with Kleine-Levin syndrome are boys, she is not typical. Clearly, more rigorous studies are needed, including 24-hour polygraphic recordings in typical patients.

The exact nature of Kleine-Levin syndrome and its relationship to other periodic hypersomnias has yet to be established. Rapid eye movement narcolepsy, characterized by the clinical tetrad of sudden sleep attacks, cataplexy, sleep paralysis, and hypnogogic hallucinations, has been rigorously studied and is clearly clinically distinct from the Kleine-Levin syndrome, although the finding of sleep-onset REM in one patient by Wilkus and Chiles[7] suggests the possibility of similar causative factors in both disorders.

In this patient, the coexistence of hypersomnia and fire setting with an episode of inappropriate sexuality suggests possible involvement of the limbic system. The patient described his fire setting and stealing as urges, and these behaviors may have represented compulsive rituals. Kelly et al[16] have treated patients with intractable obsessions and compulsions by cutting the anterior cingulate gyrus; this has been successful in some cases.

By inference, then, the cingulate gyrus, which is an integral part of the limbic system, is thought to mediate some aspects of ritualistic, compulsive behavior. The amygdala is also part of the limbic system and has rich neural interconnections to the hypothalamus; both are known to influence eating behavior and sexual behavior, which are classically disturbed in the Kleine-Levin syndrome. The hypothalamus

has neural connections to both the reticular activating system and the limbic system. The raphe nuclei are serotonin-containing neurons located in the lower midbrain and upper pons and are part of the reticular activating system; the axons of these nuclei ascend via the medial forebrain bundle (MFB) to terminate primarily, but not exclusively, in the hypothalamus. Animal studies suggest that these serotonergic raphe nuclei may mediate sleep onset and maintenance. There are two major norepinephrine pathways. The ventral pathway originating from nuclei in the brain stem also ascend via the MFB to the hypothalamus and to other portions of the limbic system. The dorsal norepinephrine pathway originating in the nucleus coeruleus ascends dorsally in the MFB to terminate in the hippocampus (also a part of the limbic system) and the cerebral cortex.[17]

Amnesia for both the hypersomnias and bizarre behavior is common in the Kleine-Levin syndrome and may relate to malfunction in the hippocampus or its interconnections within the limbic or reticular activating systems. The described advances in neurochemistry may well provide a theoretical framework for clearer understanding of the sleep disorders, particularly Kleine-Levin syndrome, as typical patients are examined and extensively studied with 24-hour EEG recordings and by evaluation of the metabolites of the putative neurotransmitters.

In conclusion, it is important that patients with Kleine-Levin syndrome often consult first with a psychiatrist for behavioral, affective, or cognitive symptoms. Kleine-Levin syndrome may represent a disorder that bridges psychiatry and neurology, and an analysis of such disorders may allow improved understanding of neuropsychiatric phenomena.

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Child Abuse

Its Relationship to Birthweight, Apgar Score, and Developmental Testing

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• Fifty-two abused and 23 nonabused children from a low socioeconomic group were studied with respect to birthweight, five-minute Apgar score, and developmental quotients. An association was found between low Apgar scores, low birthweight, poor performance on developmental testing, and child abuse. Furthermore, it was found that among children with normal birthweights, abused children tended to have lower Apgar scores and significantly lower developmental quotients. This study suggests that among this group of children, abuse and subsequent poor performance may be related not only to the socioeconomic status of the children but also to the characteristics the child brings to the parent-child relationship and to the abusive environment.

***(Am J Dis Child* 132:790-793, 1978)**

During the past few years, as a result of the increasing awareness of the problems associated with child abuse, attempts have been made to investigate the etiologic factors of this sociomedical disorder.[1] Relationships between socioeconomic conditions and abuse[2] as well as between parental psychological makeup and abuse have been drawn.[3,4] A definite association has been found between low birthweight and abuse.[5] Furthermore, it has been suggested that when faulty maternal attachment occurs in the immediate newborn period, children may be at risk for being abused.[6] Finally, other studies have shown a relationship between abuse and poor performance on developmental testing.[7] However, in these studies, differences in birthweight were not considered. The purpose of this article is to examine the relationship between child abuse, birthweight, the five-minute Apgar score, and performance on the Bayley Scales of Infant Development.[8]

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SUBJECTS AND METHODS

The subjects were drawn from a study population of both abused and nonabused children who had been involved in a prospective study on child abuse. Child abuse, which was defined in accordance with the 1969 Colorado law (Senate Bill No. 57) on reporting of child abuse, included nonaccidental trauma, neglect, and failure to thrive. The 140 subjects in the prospective study were recruited during the years 1972 to 1975. All children hospitalized at Denver General Hospital with the diagnosis of nonaccidental trauma, failure-to-thrive, or both were included in the study. The control subjects also included in that study were nonabused children of normal and low birthweight recruited from the Well-Child Clinics operated by the Denver Department of Health and Hospitals. Not all of those children were included in the current study since data on birthweight, Apgar scores, and developmental quotients were not available for all of them. Hence, the current study included only children for whom complete data were available. The group finally studied was made up of 44 boys and 31 girls who ranged in age from 2 to 30 months. Fifteen of the boys and ten of the girls had sustained nonaccidental trauma. Another 15 boys and nine girls had the diagnosis of failure-to-thrive. Two girls and one boy sustained both nonaccidental trauma and failure-to-thrive. The nonabused control group included 13 boys and ten girls.

The Apgar scores and birthweights were obtained from the hospital records. The developmental scores were obtained by the study personnel using the Bayley Scales of Infant Development either at the time the child was identified as being abused or when the nonabused controls entered the study. At the time of testing, the study personnel were aware that the children were abused or nonabused but did not know their birthweights or Apgar scores. Statistical analysis comparing the study groups was performed using analysis of variance and the chi-square test.

RESULTS

The first parameters studied were the relationships between abuse and both developmental functioning and the five-minute Apgar scores. As is given in Table 1, abused children scored significantly lower than nonabused controls on both the mental and motor portions of the Bayley Scales of Infant Development. Figure 1 also shows that abused children had lower Apgar scores than did the nonabused controls.

However, both the abused and nonabused populations consisted of

Table 1.—Developmental Quotients of Abused and Nonabused Children

	Developmental Quotients*					
	Abused (N = 52)	Nonabused (N = 23)	F	P	df_1	df_2
Mental scale	87.52 ± 18.12	106.00 ± 16.40	17.55	<.001	1	73
Motor scale	88.13 ± 19.81	104.17 ± 20.54	10.22	<.001	1	73

*Developmental quotient indicates mean score ± SD.

Table 2.—Relationship Between Birthweight and Child Abuse*

	Abused Children		Nonabused Children	
Weight, g	No.	%	No.	%
<2,500	14	27	2	8.7
>2,500	38	73	21	91
Total	**52**	**100**	**23**	**100**
Mean weight ± SD, g	2,825 ± 668		2,995 ± 418	

*F = 1.27; df_1 = 1; df_2 = 73; P > .05.

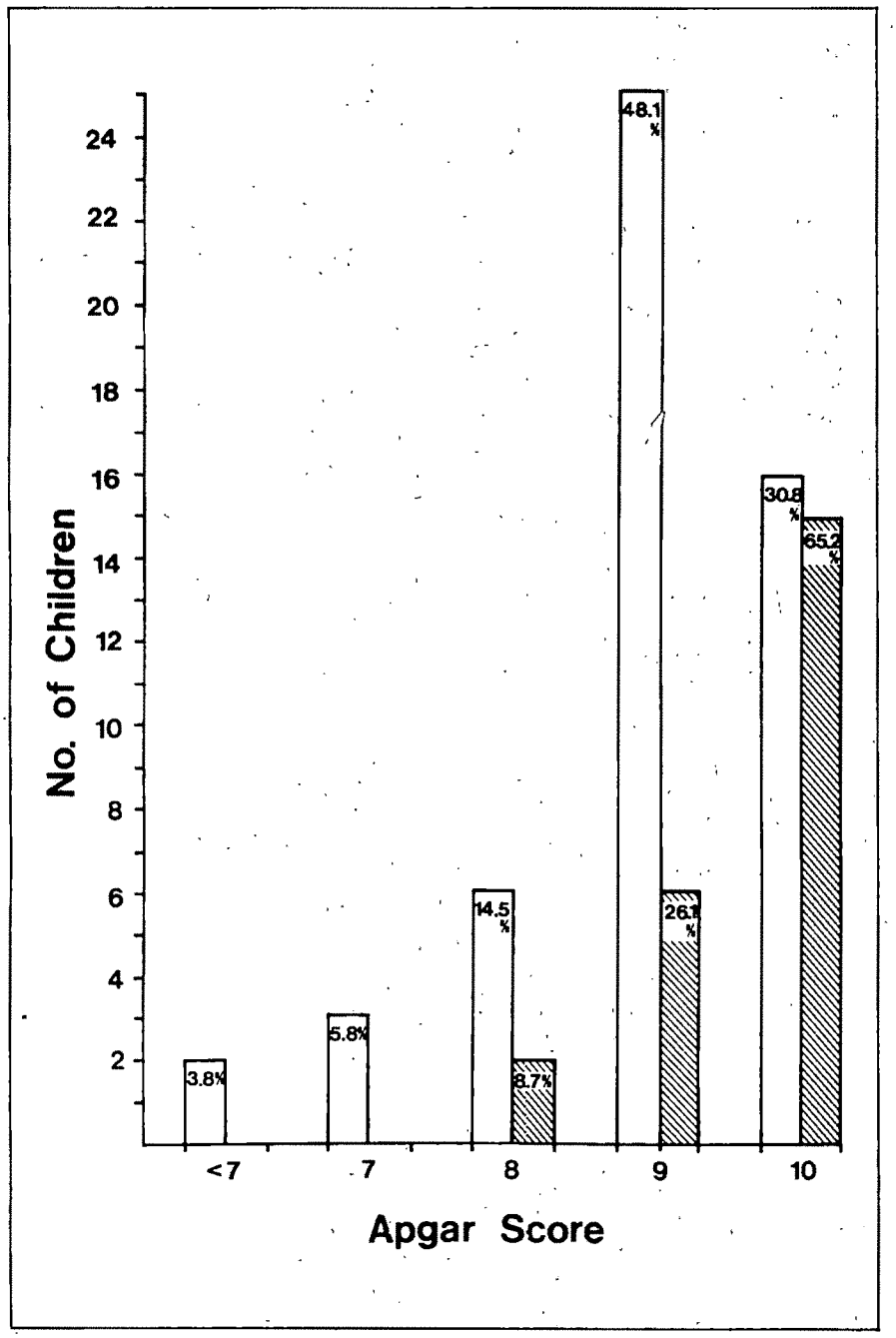


Fig 1.—Five-minute Apgar scores of abused and nonabused children. Clear bar indicates abused children; bar with diagonal lines indicates nonabused children.

children with both normal (> 2,500 g) and low birthweights (< 2,500 g). It seemed important, therefore, to examine the abused children with respect to their birthweights. The incidence of low birthweight was 27% among the 52 abused children as compared with 8.7% for the 23 nonabused controls (Table 2). The difference between these groups is not statistically significant because of the small sample. However, in a previous publication[9] in which both abused and nonabused children were drawn from the same neighborhood health program population as the current subjects, the increased number of abused children with birthweights under 2,500 g was statistically significant.

Performance on the Bayley Scales of Infant Development of abused and nonabused children with low birthweights was compared. There were no differences in developmental functioning between the two groups of children with low birthweights. However, children in both of these low birthweight groups scored much lower than children with birthweights greater than 2,500 g (Fig 2).

Next we compared the developmental quotients and Apgar scores of the nonabused and abused children with those of children with normal birthweights. In contrast to the children with low birthweights, when children with normal birthweights were compared, the nonabused children did significantly better on developmental testing than did the abused children (Table 3). As shown in Fig 3, the Apgar scores of the abused and nonabused children with normal birthweights were also different. There were more nonabused (71%) than abused children (40%) with Apgar scores of 10. These findings were

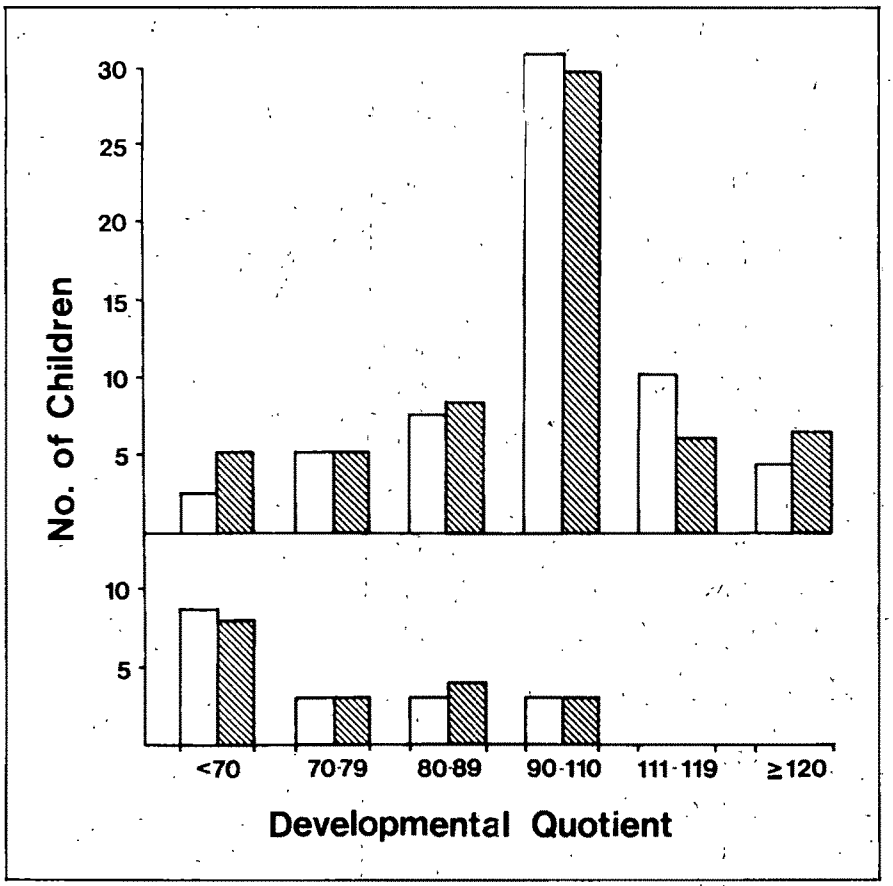


Fig 2.—Comparison of developmental quotient (DQ) and birthweight. Clear bar indicates mental DQ; bar with diagonal lines indicates motor DQ. Top, DQs of 59 children with birthweights ≥ 2,500 g. Bottom, DQs of 16 children with birthweights < 2,500 g. For children with birthweights > 2,500 g, mean mental DQ was 99.2 and mean motor DQ was 98.2. For children with birthweights < 2,500 g, these were 71.2 and 74.0, respectively. For mental scale $t = 6.27$, $df = 73$, $P < .0001$; for motor scale, $t = 4.55$, $df = 73$, $P < .0001$.

Table 3.—Developmental Quotients Among Abused and Nonabused Children With Normal Birthweights

	Developmental Quotients*					
	Abused (N = 38)	Nonabused (N = 21)	F	P	df_1	df_2
Mental scale	93.89 ± 15.57	108.67 ± 12.14	14.11	<.001	1	57
Motor scale	93.79 ± 18.40	106.24 ± 19.25	5.99	<.05	1	57

*Developmental quotient indicates mean score ± SD.

statistically significant ($\chi^2 = 5.53$; $df = 1$; and $P = .019$). Finally, there were more abused children (7.9%) with Apgar scores of less than 8.

COMMENT

Several interesting findings emerged from our study. First, we were able to show, as have other workers, that low birthweight and abuse are associated.[5,9] Second, we found that there is an association between low birthweight and poor performance on developmental testing, a conclusion that has been reported by others.[10,11] Third, we demonstrated that when abused and nonabused children with normal birthweights and from the same socioeconomic group are compared, the abused children still did significantly worse on developmental testing than did their nonabused counterparts. As has been noted earlier, previous reports evaluating developmental functioning of abused children do not distinguish abuse with respect to birthweight. Finally, there appears to be an association between lower Apgar scores and abuse, even among children with normal birthweight.

Several authors have associated child abuse and its results with poor socioeconomic conditions.[2,12] Although we agree that economic and social deprivation are among the important predisposing factors for child abuse, the current study suggests that other variables are important with respect to the developmental outcome for abused children. Our data demonstrate that abused children with normal birthweights from low socioeconomic groups do worse on developmental tests than do nonabused children of normal birthweight from the same group. This suggests that there are destructive forces peculiar to the abusive environment among the poor that are not necessarily related only to poor socioeconomic conditions.

The final finding of this study concerns the relationship between the infant's condition at 5 minutes of age and the infant's subsequent fate. Other investigators have associated lower Apgar scores with lower scores on the Bayley Scales of Infant Development.[13] The data for our total population, which includes children of both normal and low birthweights, show an appreciably lower Apgar score among the abused children than among the nonabused children. When we examined the Apgar scores of the abused and nonabused children with normal birthweights, the differences, although not as striking, were significant. Does the infant's initial distress, which the lower Apgar score reflects, influence the parents' (mother's and/or father's) ability to bond to their baby? We suggest that these infants might be less able to manifest those qualities that attract parents to their infant and so facilitate the establishment of a warm and comfortable relationship between parent and child. Thus, we suggest that if there is a failing in this attachment, the child is at greater risk of being abused and consequently of having subsequent developmental delays. These develop-

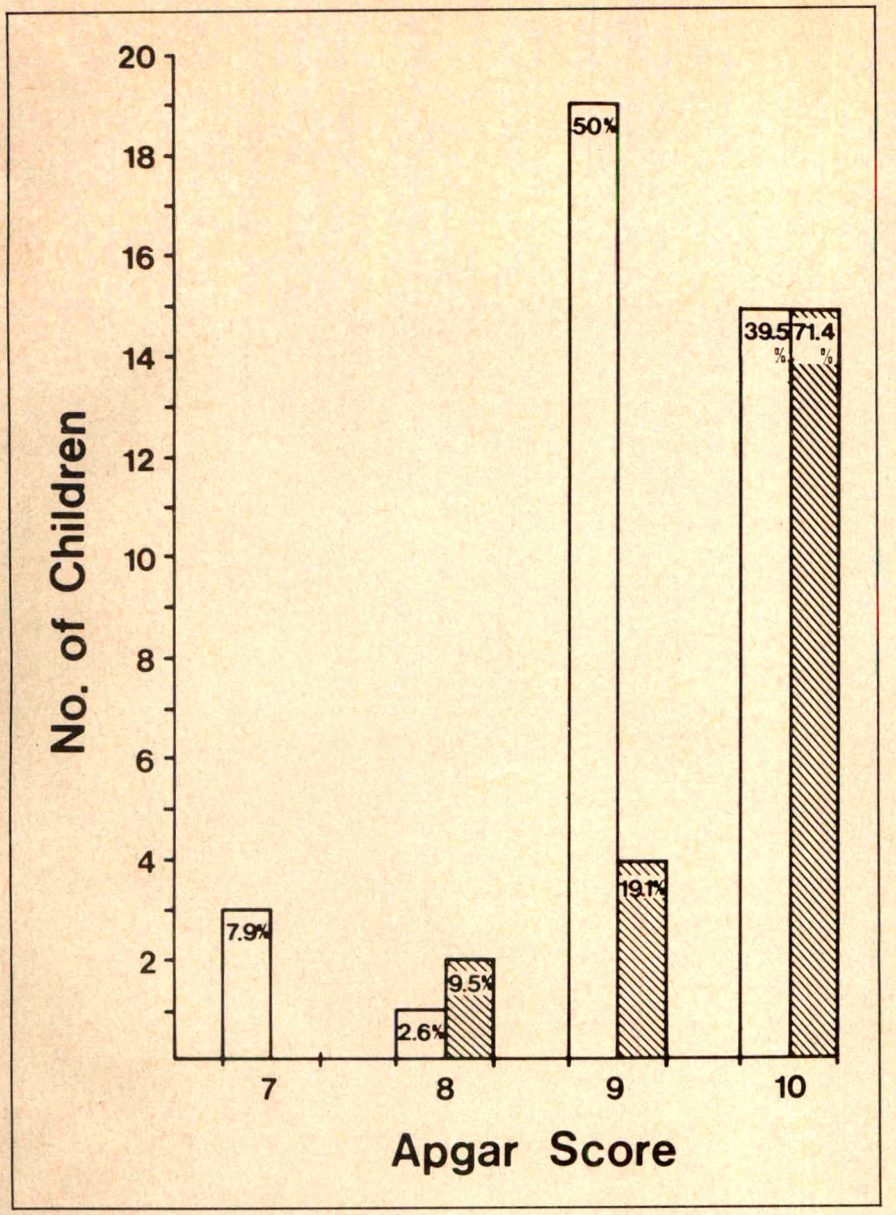


Fig 3.—Five-minute Apgar scores of abused and nonabused children with normal birthweights. Clear bar indicates abused children; bar with diagonal lines indicates nonabused children.

mental lags may, therefore, be more the product of poor attachment, inadequate stimulation, and abuse than a function only of poor socioeconomic conditions. It should also be noted that none of the children with normal birthweights had any problems that could be identified by physical examination.

If one accepts this thesis, it follows that early identification of infants at high risk for abuse (a capability we must strive to enhance) can be further improved on by attention to infants with low Apgar scores, particularly among children with normal birthweights. Gray and her co-workers[14] have sought to identify the breakdown, or lack of attachment, in the delivery room by observing the mother's response to her infant. We suggest that any child with a low Apgar rating, even with a normal birthweight, could be at increased risk for lack of maternal bonding and, therefore, under greater jeopardy for abuse. Consequently, such children and their parents should be observed closely, and support, instruction, and direction should be provided both before and after discharge from the hospital if there is any evidence for an inappropriate attachment. In this way one might be able to promote good parenting skills and reduce the chance for subsequent breakdown in parenting and later abuse.

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John R. Connell, MD, John T. McCarthy, MD, and P. A. Campbell, PhD provided criticism and review of this article, and Nancy McPherson prepared the figures.

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Elevations of SGOT, SGPT, and serum LDH have occurred in patients taking Cylert, usually after several months of therapy. These effects appear to be reversible upon withdrawal of the drug, and are thought to be manifestations of a delayed hypersensitivity reaction. There have also been a few reports of jaundice occurring in patients taking Cylert; a causal relationship between the drug and this clinical finding has not been established.

There have been reports of dyskinetic movements of the lips, face, and extremities occurring with the use of Cylert. Convulsive seizures have also been reported. A definite causal relationship between Cylert and these reactions has not been established.

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Review Article

Preadolescent and Adolescent Endocrinology: Physiology and Physiopathology

II. Hormonal Changes During Abnormal Pubertal Development

Pierre C. Sizonenko, MD

• **Based on the knowledge of the physiology of regulation of gonadotropins and gonadal steroids, basal levels of these hormones might be indicative of the etiologic factors of abnormal pubertal development. In addition, stimulatory tests may help in the diagnosis of such conditions. It is interesting that the pubertal maturation of the adrenal cortex is independent of the hypothalamic-pituitary-gonadal axis. The role of the adrenal cortex for the pubertal development remains questionable: adrenal androgens are low in isosexual precocious puberty, low in delayed adolescence, and normal in hyper- or hypogonadotropic hypogonadism. The importance of this role is doubled in congenital virilizing adrenal hyperplasia. When the disease is untreated, although adrenal androgens in excess advance bone age and hypothalamic maturation, girls remain prepubertal. When the therapeutic control is good, normal puberty occurs. The action of the adrenal androgens on growth and puberty remains to be determined.**

(*Am J Dis Child* 132:797-805, 1978)

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Physiological endocrine events occurring during normal puberty have been summarized in part I.[1] Part II will be concerned with the analysis of the hormonal data obtained during abnormal pubertal development. Some of the hormonal determinations have permitted the clarification of the mechanism of occurrence of some abnormal forms of pubertal development. With the use of very refined, specific, and sensitive radioimmunoassays, it is possible to determine basal levels of hormones as well as to analyze the endocrine gland responses to administration of drugs or hormones. Many reviews have analyzed the diagnostic procedure that should be used for correct diagnosis and treatment. Emphasis will be placed on these hormonal responses to determine their usefulness and their meaning in terms of understanding of the control of the onset of puberty in man. This article will be oriented to the pathophysiology of abnormal pubertal development.

PRECOCIOUS PUBERTY

Precocious puberty can be classified into two groups: isosexual precocious puberty, which results from the premature production of pituitary gonadotropins, and pseudoprecocious puberty, which is due to an exaggerated secretion from the gonad or the adrenal glands. In the latter instance, sexual development is independent of the mechanisms that normally control the hypothalamic-pituitary-gonadal axis.

Isosexual Precocious Puberty

True isosexual precocity is secondary to the premature activation of the normal mechanisms that control hypothalamic-pituitary activity. In most instances, sexual precocity is of unknown origin.[2,3] Central nervous system tumors are more likely to be associated with isosexual precocity in boys than in girls. Basal plasma and urine gonadotropin levels have often been found to be elevated compared with values obtained for normal children at the same age, and they are generally in agreement with values observed at a similar stage of puberty. Sleep-associated release of luteinizing hormone (LH) has been observed in patients with idiopathic and tumoral precocious puberty.[4] These findings show that patients with precocious puberty related to CNS stimulation can exhibit the normal pubertal LH pattern of augmented secretory activity that is synchronous with sleep. In one case of hypothalamic hamartoma with precocious puberty, luteinizing

hormone-releasing hormone (LHRH) was detected by immunofluorescence, suggesting an abnormal secretion of LHRH.[5] During stimulation by LHRH during idiopathic sexual precocity, increased LH responses were noted in most cases and were associated with a mature pattern of LH release that corresponded to the clinical stage of puberty.[6,7]

Plasma estradiol (E_2) levels have been determined in true isosexual precocity. Although the median values of E_2 (as well as of follicle-stimulating hormone (FSH) and LH levels) were higher than normal age-matched controls, only 50% of the individual values were greater than the upper limit of the normal range, strongly suggesting that single plasma E_2 determinations cannot be a reliable variable for diagnosis.[8,9] Sequential sampling over a month's time has shown that E_2 levels in true sexual precocity follow a sequence similar to the pattern observed in healthy pubertal girls.[8]

Isosexual sexual precocity may also be associated with congenital anomalies such as polyostotic fibrous dysplasia. In this syndrome characterized by bone lesions, café au lait spots, and sexual precocity, hyperthyroidism, gigantism, or acromegaly, hyperadrenocorticalism can be associated. The syndrome may represent a congenital, abnormal hypothalamic function with hypersecretion of releasing hormones and further stimulation of the anterior pituitary.[10,11]

Other than medroxyprogesterone that has been used as a progestational agent for many years[2,3] and as an antigonadotropic agent, cyproterone acetate has been recently used by several groups. Before 1974, many articles in the literature reported that medroxyprogesterone can arrest the development of sexual signs such as menses, breast development, and penile growth. Urinary excretion of sex steroids and gonadotropins decreases. Undesirable side effects were observed. Medroxyprogesterone acetate has a slight glucocorticoid activity that can cause signs of Cushing's syndrome and also partially suppress adrenocorticotropic hormone (ACTH) secretion. Medroxyprogesterone has a poor effect on advanced bone age, accelerated growth, and adult height prediction.[3] Cyproterone acetate has an antigonadotropic action and reduces the LH responses to LHRH stimulation.[7,12] It may also have an action at the gonadal level by depressing steroid biosynthesis[13] as it decreases plasma E_2 levels. The degree of clinical improvement of the conditions of persons with true sexual precocity receiving cyproterone as well as medroxyprogesterone has been a very controversial issue. The clinical signs of puberty have regressed in most instances, but the advancement of bone age and tall stature were not substantially affected by the therapy.[14,15] Thus, although, as for medroxyprogesterone, clinical signs of pubertal development can regress or fail to progress, the eventual compromised adult stature, characteristic of patients with sexual precocity, is not prevented. Although adrenal androgens are usually normal for chronological age, it has been noted that cyproterone acetate, which decreases the level of pituitary ACTH, induces a decrease in the levels of cortisol and dehydroepiandrosterone. This antiadrenocortical effect has been used in a preliminary fashion in the treatment of congenital virilizing adrenal hyperplasia.[16]

Pseudoprecocious Puberty

Because of the premature activation of the hypothalamic-pituitary-gonadal axis, isosexual precocity eventually leads to full sexual maturation given sufficient time. Conversely, in pseudoprecocious puberty, the hypothalamic-pituitary axis is not involved. Some cases of pseudoprecocious puberty can be due to gonadotropin-producing tumors that are malignant: chorioepitheliomas, teratomas, or hepatomas. These tumors produce human chorionic gonadotropin (HCG), some compounds with LH activity, or subunits of HCG such as β-HCG. As a result of the LH-like effect of the gonadotropin produced, activation of the Leydig's cells and increased testosterone production occur.

On the other hand, testicular or ovarian tumors will mainly produce high plasma levels of androgens or estrogens, with low levels of gonadotropin. High testosterone or Δ^4-androstenedione levels have been observed[3] when Leydig's cell tumors were present. Normal-to-elevated levels of urinary estrogens and plasma E_2 have been found in cases of granulosa cell tumors. In luteinizing tumors, progesterone and pregnanediol levels are also elevated.

In some patients, heterosexual maturation has been observed: feminizing testicular adenoma or virilizing ovarian tumors (arrhenoblastomas). The most common form of pseudoprecocious puberty is the adrenogenital syndrome, particularly in its congenital, virilizing form. This point will be developed later. Isosexual pseudoprecocious puberty in girls and heterosexual precocious puberty in boys as a result of estrogen-producing adrenal tumors are rarely observed.

Incomplete Sexual Precocity

Incomplete sexual precocity represents either premature thelarche (premature breast development) or premature adrenarche (premature growth of pubic and/or axillary hair) without the development of any other sexual secondary characteristics. The reason for such premature development of breasts or sexual hair is not understood. In premature thelarche, basal plasma gonadotropin levels may be within the normal range[6,17] or slightly elevated. During the LHRH stimulation test, FSH release is very often similar in these girls to the response observed in normal girls during the first year of life[6] but may be similar to normal prepubertal girls. The LH response is lower than that observed in normal girls less than 1 year of age. Plasma E_2 levels are usually within the normal range for age, although in some cases, high levels have been observed.[9,17] Hence, in some cases, elevated levels of plasma E_2 might have been a factor in the development of breast tissue. Free E_2 levels might also be higher in girls with premature thelarche than in normal prepubertal girls.[18] This hypersecretion of estrogens may also be related to transient sexual precocity that is due to follicular cysts of the ovary in the prepubertal girl. In some

cases, the source of the estrogens might also be the luteinized Graafian follicles that are frequently observed in the ovaries of prepubertal girls.[19] However, premature thelarche may represent inappropriate sensitivity of the breast tissue to normal levels of estrogens.

Gynecomastia

Although it is not a symptom of precocious puberty, gynecomastia in the male adolescent is often seen, and its physiopathology is unknown. Plasma estrone (E_1) and E_2 levels observed in boys with gynecomastia were either similar[17,20,21] or transiently elevated[22,23] when compared with those of a group of healthy boys of the same age. A substantial increase of the level of E_2 may occur with the onset of gynecomastia and the E_2-testosterone ratio is often increased. Serum prolactin level is not elevated in these cases.[22]

Premature Adrenarche

Hormonal changes during premature adrenarche were discussed in the first part of this review. Plasma levels of dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S) are high or are in the high-normal range (Fig 1) for chronological age.[24,25] Bone age is usually advanced in this condition, and DHEA and DHEA-S levels correspond to the bone age, not to the chronological age. Dehydroepiandrosterone is thought to have a weak androgenic effect, and sexual hair growth as well as advanced bone age maturation are supposedly a result of peripheral conversion of DHEA to testosterone.

CONGENITAL VIRILIZING ADRENAL HYPERPLASIA AND THE EFFECT OF EXCESSIVE SECRETION OF ADRENAL ANDROGENS ON PUBERTAL DEVELOPMENT

Because excessive androgens (in particular DHEA and DHEA-S)[26] are being secreted in untreated congenital virilizing adrenal hyperplasia, this disease should be a model of the influence of adrenal androgens on pubertal development. As yet, the situation is unclear. A recent symposium has tried to establish known facts.[27] Excessive androgens in untreated patients produce accelerated growth and advanced bone age.[28] This may be associated with the maturation of the hypothalamic-pituitary-gonadal axis. When treatment is introduced after a bone age of 12 years, precocious puberty sometimes develops with an increase in the levels of plasma LH and FSH, an increase in testicular size in boys, and the occurrence of menstruation in girls. The release of pituitary gonadotropins subsequent to androgen-suppressive cortisone therapy is responsible for the precocious pubertal changes observed in these late-treated patients. A normal maturational pattern of gonadotropin response seems to be found in LHRH stimulation in correctly treated patients. Although bone age can be advanced in untreated patients with increased adrenal androgens, the pattern of gonadotropin release after LHRH is administered to untreated patients remains the same as that of prepubertal children. This suggests inhibition either of hypothalamic LHRH production or of pituitary gonadotropin synthesis and release by excessive adrenal androgens.[29] This observation contradicts the finding of an increased FSH production, which can be questioned because of the methods used.[30] With suppression of adrenal androgen secretions, the pattern of gonadotropins becomes progressively of pubertal type.[29]

It is not clear, however, whether the prepubertal girl affected with congenital virilizing adrenal hyperplasia, with a bone age less than 10 years old, exhibits a prepubertal female pattern of FSH release (higher FSH release than in a normal pubertal girl).[31-33] Normal responses of FSH and LH after LHRH therapy have been observed also in girls maintained on doses of suppressive glucocorticoids appropriate to body surface area.[34,35] These findings suggest that excessive androgen production is the major factor contributing to delayed onset of normal menstruation and cyclicity.[31,35]

The hypothalamus matures normally, and there is a lack of effect of intrauterine, neonatal, and postnatal androgen excess.[31] On the average, menarche is delayed.[30,37-39] With adequate therapy and appropriate doses of corticosteroids, pulsatile output of LH is noted when the patient is asleep, and menstruation is normal. In patients in whom therapeutic control has been poor, prepubertal or atypical patterns are observed. In patients in whom therapeutic control is maintained at reasonable but not optimal levels, the hormonal patterns observed are within the broad range of normal.[37-40] The clinical response of these latter patients in respect to menarche and menstrual history is indicative of minor dysfunction.

The association of abnormal ovaries and congenital adrenal hyperplasia has been reported previously and summarized recently.[41] In untreated cases of congenital virilizing adrenal hyperplasia, histological features of polycystic ovaries can be observed,[42] ie, a decreased number of follicles and peripheral scleroses. These findings are seen in the presence of incomplete suppression of androgen secretion and anbormalities of gonadotropin secretion (increased levels of circulating LH). The etiologic factors may be based on the exposure of the hypothalamus and/or the ovary to excessive androgens, or in the latter case, to excessive LH as well, in prenatal and postnatal life. The increase in the LH level could be secondary to the androgen excess.

In male patients, testicular atrophy occurs and is attributed to hypogonadotropic hypogonadism caused by the gonadotropin-suppressing effect of the high plasma levels of adrenal steroids. However, bilateral testicular masses have been reported for many years in untreated patients. Although some authors have called these tumors ectopic adrenal rests, others have believed that they represent Leydig's cells. There has been, up to now, no agreement on the origin of these tumors. Most of the confusion results from the great similarity between the histological appearance of adrenal rests and that of Leydig's cells. Some of these tumors can be stimulated by ACTH and suppressed by dexamethasone.[43] Normal spermatogenesis in four adult males with congenital adre-

nal hyperplasia after discontinuation of therapy was recently reported.[44] These patients are fertile despite abnormal steroid findings and despite relatively small testes in two of them. If the normal spermatogenesis of these patients is related to the earlier corticosteroid treatment, it would imply that treatment with corticosteroids is necessary for the pubertal induction of spermatogenesis but not for the maintenance of normal spermatogenesis. Normal levels of testosterone were found, as well as of FSH and LH, but high levels of E_2 and E_1 were observed. These levels did not induce gynecomastia, and no abnormality of plasma FSH and LH levels was apparent, even after LHRH, suggesting that there is a resistance to estrogens at the hypothalamic and peripheral levels.[44]

Cyproterone acetate, which has been reported in preliminary data to decrease ACTH-dependent corticosteroid secretion, might be of some help in the therapy of adrenal congenital hyperplasia. However, it should not be used at puberty or later since it has an antigonadotropic effect, as shown by the decreased response of LH to LHRH in isosexual precocious puberty.[7] However, nothing is known of the long-term effect of cyproterone acetate in prepubertal children.

HYPOGONADISM

Two hypogonadic states have been described based on the level of the defective secretion: if the gonads are responsible for the absence of pubertal development, the hypogonadism is known as hypergonadotropic, and its condition is easily recognized. Conversely, if the secretions of the hypothalamus or the anterior pituitary are defective, the hypogonadism is hypogonadotropic. The latter condition is difficult to recognize and needs further investigation.

Hypergonadotropic Hypergonadism

This can be easily detected during early adolescence, as elevations of both FSH and LH levels can be found secondary to deficient steroid production by the abnormal or absent gonads. Turner's syndrome in girls and anorchia in boys represent the ultimate state. Klinefelter's syndrome represents essentially an abnormality of the seminiferous tubules in relation to the XXY chromosome composition and with a secondary increase of FSH levels. Elevations of basal LH or FSH levels have been detected after the age of 10 to 11 years in these conditions. Responses to LHRH usually have been exaggerated after 12 years of age, but large individual variations have been observed.[45,46] In Turner's syndrome, in the presence of normal basal levels, elevated responses of LH and FSH may be observed before puberty.[47] Pulsatile secretion of gonadotropins in adolescent patients with the syndrome of gonadal dysgenesis (14 LH peaks during 20 hours with fewer, broader FSH peaks) seems to be unrelated to ovarian secretion and is probably of hypothalamic origin.[48] Girls with gonadal dysgenesis have a pattern of secretion of FSH similar to that of normal girls but at a much higher level: between birth and two years and at puberty.[49] The whole pattern very likely relates to a change in sensitivity of the hypothalamic receptors, either because of some intrinsic influences or secondary to peripheral circulating sex steroids, particularly to adrenal androgens, as gonadal secretions are minimal in these patients. Adrenarche and the secretion of adrenal androgens occur normally in agonadal patients (Fig 2).

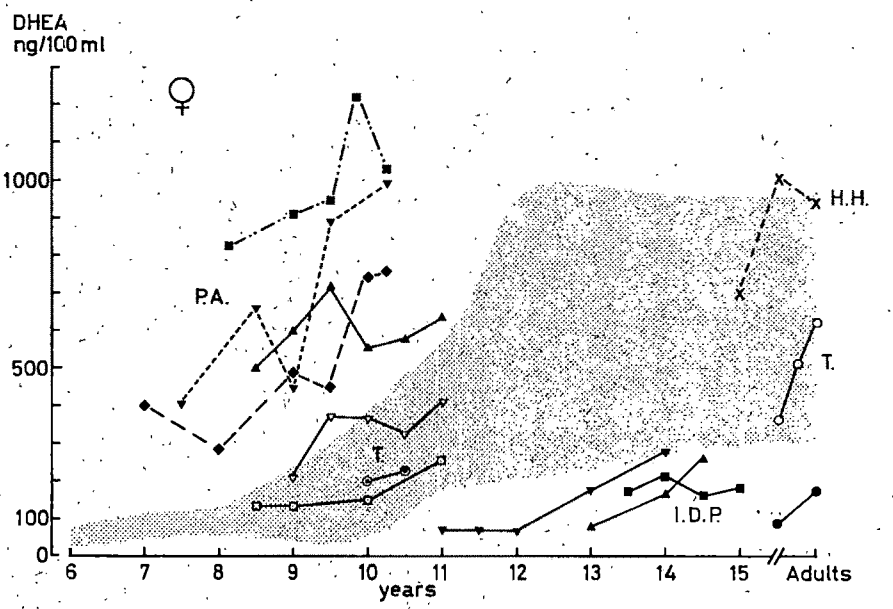


Fig 1.—Plasma DHEA concentrations during pubertal development in four types of female patients compared with normal range (shaded area). PA indicates premature adrenarche; T, Turner's syndrome; IDP, idiopathic delayed puberty; and HH, hypogonadotropic hypogonadism.

In summary, elevated levels of gonadotropins should occur at some time during the development of a child with abnormal gonads. Therefore, plasma determinations of FSH and LH at six-month intervals may aid, as will the LHRH stimulation test when basal levels of FSH and LH are normal, in the differential diagnosis of hypergonadotropic states.

Hypogonadotropic Hypogonadism

This is due to a permanent deficiency of hypothalamic and/or pituitary secretions of gonadotropins, whereas delayed sexual maturation (idiopathic delayed puberty) is due to a retarded activation of the hypothalamic-pituitary-gonadal axis. Some investigators have reported that children with hypopituitarism cannot always be distinguished from normal children. However, others have observed lower levels of LH and/or of FSH in patients with hypopituitarism. Basal levels, in fact, do not permit distinction between hypogonadotropic hypogonadism and constitutional delayed adolescence. It is clear that the diagnosis is easier if multiple hormone deficiencies, a de-

fect in smell, or other genetic defects are also present. In anosmia, aplasia or hypoplasia of olfactory bulbs and tracts appears to be responsible, and gross defects of the hypothalamus have been noted. Isolated gonadotropin deficiency may also exist without these associated disorders. The diagnosis is therefore often difficult.

Since determination of basal levels of urinary or serum gonadotropins appears to be of limited value in the diagnosis of hypogonadotropic states, stimulatory and inhibitory tests have been developed over the last ten years. Several principal methods have been devised to investigate the secretion of the gonadotrophs: use of antiestrogens or antiandrogens that act at the hypothalamic level, administration of LHRH that stimulates the pituitary secretion of gonadotropins, and the search for sleep-induced gonadotropin surges that appear at puberty. The serum concentrations of plasma prolactin, basal and stimulated gonadal steroids, and adrenal androgens may also be of value.

Use of Antiestrogens and Antiandrogens.—Several substances have been used rather unsuccessfully for the differential diagnosis of idiopathic delayed puberty (or delayed adolescence) and hypogonadotropic hypogonadism. The main substance used has been clomiphene citrate, an analogue of the nonsteroidal estrogen, chlorotrianisene. In normal men, clomiphene citrate increases the level of serum gonadotropins. In most cases of hypogonadotropic hypogonadism, clomiphene did not induce an increase of FSH and/or LH and testosterone levels. In normal prepubertal children, no increase in the level of gonadotropins is noted after the administration of clomiphene. Therefore, this test has to be interpreted with caution because of the change demonstrated of the sensitivity of the pubertal gonadal hypothalamic feedback mechanism during pubertal development in man.[50] In hypogonadotropic hypogonadism, the absence of a stimulatory effect of clomiphene is therefore nondiagnostic (Fig 1). Flutamide, a nonsteroid antiandrogen, has also been tried without success.[51] More recently, the antiandrogen action of

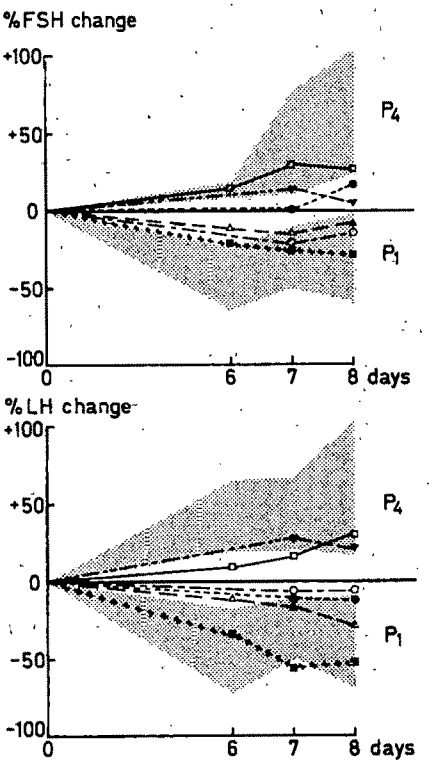


Fig 2.—Percentage of changes of plasma LH and FSH levels in male hypogonadotropic hypogonadism compared with normal responses to clomiphene citrate (100 mg/day from day one to day seven), in five prepubertal control (P_1) and five control pubertal boys (P_4). Shaded area indicates normal range.

spironolactone has been noted to cause an increase of FSH and LH levels in boys with delayed onset of adolescence.[52] These drugs may prove to be useful for follow-up testing to establish the normal evolution of delayed puberty.[53]

LHRH.—The availability of synthetic LHRH has made possible the evaluation of pituitary gonadotropic responsiveness at different stages of sexual maturation and in disorders involving the hypothalamic-pituitary-gonadal axis. According to reports by several groups of investigators, heterogenous responses to LHRH have been noted in hypogonadotropic hypogonadism. Although there is a tendency to observe higher responses of FSH and LH in hypothalamic disease than in pituitary disease,[54,55] it is usually impossible to distinguish clearly between hypothalamic and pituitary causes of hypogonadotropic hypogonadism.[56] Moreover, responses may vary from one patient to another. Isolated gonadotropin deficiency is probably a heterogenous syndrome.[57,58] In some cases, such as of the fertile eunuch, a possible defect of one gonadotropin (FSH or LH) or a β-subunit of a gonadotropin could be hypothesized.

To have a more valid LHRH stimulation test, several protocols have been suggested, including the use of LHRH before or after seven days of administration of clomiphene. In hypogonadotropic hypogonadism, the use of clomiphene may increase the LHRH-induced LH peak, whereas FSH does not change.[59] Several hours of infusion of LHRH or prolonged administration of LHRH[60,61] may induce a normal response to LHRH. However, it is interesting that plasma responses of levels of LH and FSH to luteinizing hormone-releasing factor (LRF) are positively correlated with the integrated basal levels of LH and FSH, and no substantial difference exists in mean basal LH levels and responses to LRF among patients with pituitary tumors, hypothalamic diseases, or isolated gonadotropic insufficiency. The response to short-term, single injection of LHRH appears to more directly reflect basal gonadotropin levels than disease category.[62] Moreover, comparison of responses of LH and FSH to LHRH in reported cases of idiopathic delayed adolescence and hypogonadotropic hypogonadism shows a large overlap of values, which does not allow any diagnostic conclusion. In overt panhypopituitarism, dissocated responses are also observed affecting LH, FSH, or both. All these discrepancies found with the use of LHRH for stimulation have made this test very unreliable.

Episodic Secretion of Gonadotropins.—The search for sleep-associated episodic secretion of gonadotropins in delayed puberty would theoretically be useful to differentiate constitutional delayed adolescence from hypogonadotropic hypogonadism. However, such episodic discharges should be able to be differentiated from fluctuations in the daily output of gonadotropins and in the concentrations of serum FSH and LH in the prepubertal individuals. In fact, variability of plasma levels of FSH and LH affects the

potential use of such a diagnostic procedure in hypogonadotropic subjects. Moreover, clinical and laboratory heterogeneity in idiopathic hypogonadotropic hypogonadism also has been observed when sleep-associated episodic secretion of LH, FSH, and testosterone has been studied.[63] In some patients, no episodic gonadotropin secretion has been found. In others, substantial sleep-related gonadotropin pulses were associated with the highest plasma testosterone levels, the best responses to LHRH, and the most differentiated testicular tissue on biospy specimens. It has been concluded that in some cases of hypogonadotropic hypogonadism, the pubertal maturational process has not been achieved and that the heterogeneity of the syndrome could be due to differences in degrees of LHRH deficiency.

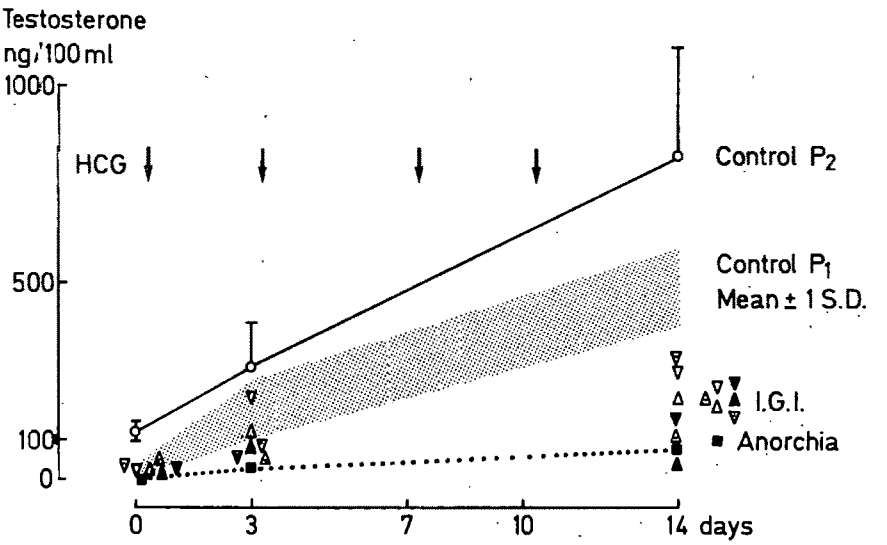


Fig 3.—Plasma testosterone response tc HCG administration (5,000 IU/sq m, indicated by arrow) in six controls at each stage of puberty (P, indicates absent signs of puberty; P_2, early signs of puberty) and in pathological conditions (triangles indicate isolated gonadotropin insufficiency [IGI]; solid squares, anorchia).

Prolactin Secretion.—Because hypersecretion of prolactin induces hypogonadism with galactorrhea in both sexes, the possibility that excessive prolactin secretion causes delayed puberty has been discussed.[64] Possible microadenoma of the pituitary has been suggested as a cause. High levels of prolactin might inhibit gonadotropin action at the gonadal level. However, in the case of delayed puberty, hyperprolactinemia may also have an inhibitory effect on the synthesis and secretion of gonadotropins. Prolactin should be measured in cases of delayed puberty.

Basal and Stimulated Gonadal Steroids.—Sex steroid hormones, secreted either by the ovary or the testis, can be studied either basally or after stimulation with HCG. Urinary excretion of 17-ketosteroids, 17-ketogenic steroids, or more precisely, conjugates of steroids such as T-glucuronide have been useful in investigating delayed puberty and hypogonadotropic hypogonadism.

Radioimmunologic or competitive protein-binding methods for assay of sex steroids have made more practical the measurements of hormone levels in plasma. After a bone age of 13 years is obtained both in boys and girls, low levels of urinary or plasma sex steroids similar to the prepubertal range suggest hypogonadism. Similar low levels are observed in persons with anorchia. In Klinefelter's syndrome, testosterone levels achieved at puberty are in the lower range of normal. In females with hypogonadotropic hypogonadism or Turner's syndrome, levels of E_2 are prepubertal.

In idiopathic delayed puberty, testosterone and E_2 are in the prepubertal range. Therefore, it might be difficult to differentiate this condition from hypogonadotropic hypogonadism. However, basal plasma levels are not decisive, and the use of stimulation tests has been proposed. The most common stimulation test suggested for hypogonadism has been HCG stimulation of the gonads or their remnants. Human chorionic gonadotropin acts in the male patient like LH does, and it has a similar stimulating effect on Leydig's cell secretion. Preliminary studies have shown that urinary testosterone excretion increased within four to six days after the intramuscular administration of one dose of HCG, 5,000 IU/sq m of body surface area.[65] Several protocols concerning HCG administration of different duration (one to 14 days) have been presented, the results of which have been summarized in other reviews. It is likely that the one-day test explores the immediate function of the Leydig's cells, whereas a longer test would also explore the capacity for multiplication and development of Leydig's cells. In anorchia, absent response of testosterone to HCG has been noted.[65-67] In hypopituitarism and hypogonadotropic hypogonadism, diminished response of plasma testosterone to HCG has been noted by several groups,[68-72] including our own (Fig 3). With more prolonged HCG stimulation, a normal testosterone response can be restored.[67-68] In some cases of hypogonadotropic hypogonadism, it has been shown that plasma testosterone levels can equal the testosterone increase observed in the normal subject, providing that the patients had been previously exposed to exogenous gonadotropins.[68] In panhypopituitarism, the absence of growth hormone might explain the low responses observed in these cases.

In the female, the ovary can respond to human menopausal gonadotropins. The administration of HCG in prepubertal and pubertal girls has been very limited because of the potential development of hemorrhagic cysts of the ovary.

In summary, both males and females with hypogonadotropic hypogonadism can respond appropriately to prolonged gonadal stimulation if the gonads are present. In bilateral cryptorchidism, conflicting results have been obtained. Several authors

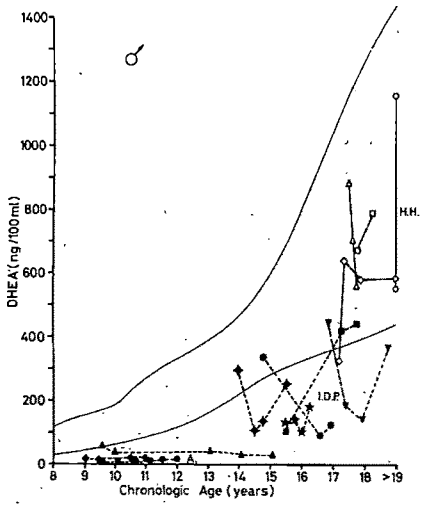


Fig 4.—Plasma DHEA concentrations during pubertal development in three types of male patients. Open symbols (HH) indicate hypogonadotropic hypogonadism; solid symbols (IDP), idiopathic delayed puberty. At bottom left, closed symbols (A) represent three cases of Addison's disease.

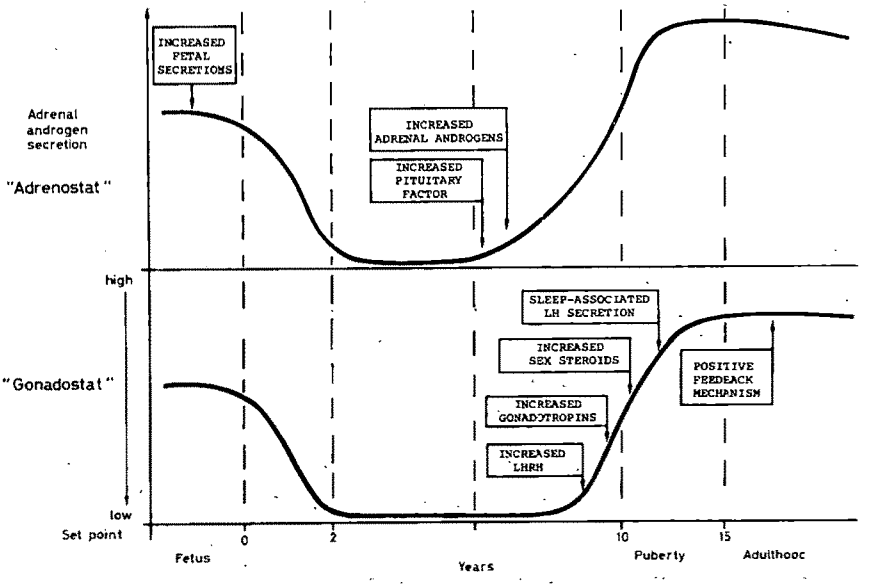


Fig 5.—Current concepts of maturation of "gonadostat" and secretion of adrenal androgens, or "adrenostat" during infancy, childhood, and pubertal development.

found no differences in the testosterone responses between normal boys and cryptorchid boys at the same stage of puberty.[73] Other groups have observed decreased testosterone responses to HCG, both in unilateral and bilateral cryptorchidism.[74] It has been suggested that bilateral cryptorchidism could be caused by hypogonadotropic hypogonadism.[68] Reduced LH response to LHRH was observed by some groups in unilateral and bilateral prepubertal cryptorchids. Conversely, in bilateral cryptorchidism with low counts of spermatogonia when a testicular biopsy specimen was taken, FSH response to LHRH was increased before puberty.[75] These findings suggest that a selective increase of the level of FSH in response to the level of LHRH is due to an actively involved, negative-feedback mechanism between inhibin, produced by the seminiferous tubule and the prepubertal pituitary. Increased basal levels of FSH have been observed in pubertal boys with bilateral cryptorchidism or unilateral cryptorchidism, with or without compensatory testicular hypertrophy.[76,77]

Treatment of nephrotic syndrome in prepubertal boys with immunosuppressive drugs like cyclophosphamide, azathioprine, or chlorambucil has also induced oligospermia or aspermia and abnormalities of testicular histology as observed in the same patients during adulthood.[78-81] Girls seem to be less affected by chemotherapy than boys, and their pubertal development appears to be normal.[79,81,82] It is important to remember, particularly for the treatment of nephrotic syndrome, that immunosuppressive drugs could affect future fertility of boys.

ADRENAL ANDROGENS AND ABNORMAL PUBERTAL DEVELOPMENT

Because recent data indicate the existence of a different mechanism for activation of adrenarche, analysis of findings concerning adrenal androgen secretion in different abnormal pubertal conditions might be of interest. In patients with Turner's syndrome[83] or isolated gonadotropin insufficiency, 84 normal levels of plasma DHEA and DHEA-S have been found (Fig 3 and 4). On the contrary, low plasma DHEA concentrations have been found in idiopathic delayed puberty. In Addison's disease, very low levels of DHEA have been observed (Fig 4). The latter findings, as well as the ones observed in premature adrenarche, strongly suggest that the hypothalamic-pituitary-cortical androgen axis is independent of the hypothalamic-pituitary-gonadal axis. As discussed previously, it is possible that adrenal androgens, through adrenarche and their interconversion to testosterone, dihydrotestosterone, E_1, and E_2, affect the onset of the gonarche or gonadal puberty. It is still questionable whether puberty is delayed in patients with Addison's disease. The association of Addison's disease with hypogonadotropic hypogonadism has been observed and must be ruled out[85,86] before the question can be answered.

CONCLUSIONS

Puberty is a very complex phenomenon in which maturation of many systems occurs with concomitant hormonal and metabolic changes; therefore, any pubertal disturbances should be thoroughly investigated. In both parts of this review, stress has been put on the physiological and pathophysiological hormonal changes observed during normal and abnormal puberty. The mechanism of the onset of puberty has been only very superficially discussed. It is believed that the maturation of the hypothalamus is related to the "gonadostat."[87]

During infancy, the sensitivity of the gonadostat to negative feedback of sex steroids seems to be low. It increases during childhood and then decreases again at the time of puber-

ty, allowing for increased secretion of gonadotropins, stimulating growth of the gonads, and secretion of sex steroids. Pubertal characteristics appear. Simultaneously, spermatogenesis occurs in boys; in girls, the ovary and its follicles mature. The positive-feedback mechanism inducing the ovulatory surge of LH after a sharp increase of E_2 appears two to 2½ years after menarche (Fig 5). Three to five years before gonarche, ie, the pubertal maturation of the gonads, the secretion of adrenal androgens (which was high during fetal life because of substantial secretion from the fetal adrenal zone) increases, inducing adrenarche independently of gonarche. This activation of the androgenic zone of the adrenal cortex is very likely under the stimulation of an unknown pituitary factor, different from ACTH, which is, however, necessary for the priming of the adrenal cortex. Which hypothalamic factor affects the secretion of a possible pituitary factor? What regulates the secretion of both these factors? All these are unknowns that, when defined, will bring more information on control of onset of puberty.

(This is part 2 of a two-part article. Part 1 appeared in July.)

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Nonproprietary Name and Trademark of Drug

Azathioprine—*Imuran.*

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Resident Seminar

Complications of Corticosteroid Therapy

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• The complications of corticosteroid therapy in children are protean. Perhaps the most important of these are adrenal insufficiency after withdrawal of steroids, immunosuppression, and growth failure. The physician who is caring for a child receiving corticosteroids must be aware of these common complications as well as the many less frequent side effects, such as cataracts, pseudotumor cerebri, pancreatitis, and steroid myopathy, to name a few. In all children, the risk of using corticosteroids should be weighed carefully before therapy with these agents is begun.

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Since their introduction more than two decades ago, corticosteroids have been used in the management of a wide variety of diseases. They have considerably reduced the morbidity and mortality in children suffering from nephrosis, leukemia, asthma, rheumatoid arthritis, and many other diseases. However, the complications of steroid therapy are protean and they may do more harm than the underlying disease for which they are prescribed. It is the purpose of this article to review the more important complications of steroid therapy in the pediatric patient (Table).

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OPHTHALMOLOGIC COMPLICATIONS

Serious and often irreversible ophthalmic complications have occurred after both systemic and topical administrations of corticosteroids. These complications include glaucoma, posterior subcapsular cataracts, bacterial and fungal infections of the eye, and exacerbations of herpes keratitis.

Steroids applied to the eye or given systemically may produce increased intraocular pressure within a few days of starting therapy. Patients with a positive family history for glaucoma may be at increased risk for this complication. The ocular hypertensive effect seems to be due to decreased aqueous outflow. This complication is dose-related and intraocular pressure usually returns to pretreatment levels with cessation of therapy.[1]

In 1960, Black et al[2] first reported posterior subcapsular cataracts in association with long-term steroid therapy. Kobayashi et al[3] observed posterior subcapsular cataracts in 28% of the nephrotic children receiving steroids. More recently, Fine et al[4] reported 41 cases of posterior subcapsular cataracts among 69 children during the first two years of steroid therapy after renal transplantation. The incidence of cataracts in the first posttransplant year increased with increasing corticosteroid dosage, and four patients had sufficient visual impairment to require cataract extraction.[4] Posterior subcapsular cataracts secondary to steroid therapy are much more frequent in children than in adults.[5] Although cataract growth usually ceases when steroids are stopped, the damage is irreversible.[1]

Corticosteroids may activate dormant herpes keratitis and increase the risk of fungal and bacterial infections of the eye.[1]

CNS COMPLICATIONS

The best known CNS complication of corticosteroid therapy is pseudotumor cerebri. This occurs more commonly in children, although isolated cases in adults have been reported.[6] In a review of 28 cases of pseudotumor cerebri associated with steroid therapy in children, 15 of the patients had been receiving triamcinolone. The average duration of therapy prior to onset of symptoms was 2½ years, although it has occurred within five months of starting steroids and as late as seven years thereafter.[7]

Pseudotumor cerebri associated with steroid therapy may be secondary to a "relative" adrenal insufficiency. In practically all cases reported, the syndrome develops when the steroid therapy is being modified by either a decrease in dosage or a change to another compound. Pseudotumor cerebri has been reported in association with Addison's disease.[7,8] In addition, 16 children with pseudotumor cerebri in whom no underlying condition was detected have shown resolution of their clinical manifestations and a decrease in CSF pressure to the normal range with corticoste-

roid therapy. Four of these children had failed to respond to repeated lumbar puncture prior to the initiation of corticosteroid therapy.[9]

These findings then create a dilemma for the pediatrician treating a child with steroid-associated pseudotumor cerebri. Should the steroids be increased, decreased, or kept at the same dosage? If the patient is receiving triamcinolone diacetate, it has been recommended that another corticosteroid be substituted. Reassuringly, Gordon and Kelsey[8] found that no patient in whom steroid therapy was continued had evidence of increasing severity of symptoms or failed to have a spontaneous remission. This is particularly important when the physician is dealing with a child in whom steroid therapy cannot be stopped, such as the child with congenital adrenal hyperplasia.

HEMATOLOGIC COMPLICATIONS

Corticosteroids will increase the total WBC count, with an increase in the percent neutrophils and a decrease in the percent monocytes, lymphocytes, and eosinophils.[10] John[11] studied ten children who received steroids for a variety of nonhematologic diseases. He found total WBC counts of greater than 20,000/cu mm in eight of the ten children. The WBC counts remained increased throughout therapy, but returned to normal within one week of stopping therapy. Total neutrophil counts were greater than 14,000/cu mm in nine of ten patients as well.[11] Studies in nephrotic patients have also shown that the higher the prednisone dosage, the greater the increase in the total WBC count.[12] The neutrophils in the peripheral blood are divided into two pools: the circulating granulocytic pool and the marginating granulocytic pool. Steroids are thought to increase the neutrophil count by shifting the neutrophils from the marginating pool to the circulating pool.[13]

Dale et al[13] have demonstrated that patients given prednisone on alternate days have a normal neutrophil and monocyte count on the day off prednisone, but show transient neutrophilia and monocytopenia within four hours after an oral dose of prednisone. Using a cutaneous skin-window as a model, they have also shown that the neutrophil response at the site of tissue injury is normal in the patient on alternate day therapy, but the monocytic response is suppressed.[13]

The decrease in eosinophil count in the steroid-treated patient is believed to be due to a reversible sequestration in the reticuloendothelial system, and to decreased marrow release. The foreign body-induced eosinophilic response is also suppressed, perhaps due to stabilization of the lysosomal membranes and decreased histamine release. Other hematologic effects of steroids include increased erythropoiesis and thrombocytosis.[10]

Corticosteroid-induced purpura resembles "senile" purpura. This purpura usually occurs on extensor surfaces, dorsum of the hand, and radial aspect of the forearm. It is thought to result from a loss of dermal collagen and elastin with subsequent shearing of small dermal vessels. The purpuric lesions are usually large and may persist for weeks.[10]

GASTROINTESTINAL COMPLICATIONS

Gastrointestinal complications that have been associated with corticosteroid therapy include peptic ulcer, pancreatitis, and hepatomegaly. Although it has generally been thought that the administration of steroids increases the risk of peptic ulcers, proof of this in controlled human studies is lacking. Patients with rheumatoid arthritis who are receiving corticosteroids have a high incidence of peptic ulcer disease, but these patients are often taking other ulcerogenic drugs, such as salicylates, phenylbutazone, and indomethacin. It is of interest that patients with ulcerative colitis and chronic skin diseases who receive corticosteroids do not have an increased incidence of peptic ulcers, and peptic ulcers are not a common complication of Cushing's disease.[14]

Recently, Conn and Blitzer[15] reviewed a large number of controlled investigations of steroid therapy in adults to see if, indeed, steroids increase the risk of ulcer disease. They found no statistically significant difference in the incidence of peptic ulcers between controls and steroid treated groups in 32 investigations representing more than 5,000 patients. In addition, they found that the patients with "steroid-induced" ulcers were no more likely than controls to have hemorrhage or perforation from their ulcers.[15]

Pancreatitis is a rare disease in children and when in 1957, Baar and Wolff[16] reported two cases of acute hemorrhagic pancreatitis in steroid-treated children, steroids were strongly implicated as the cause. Stumpf et al[17] found pancreatic lesions in 44 of 53 rabbits at autopsy after hydrocortisone therapy, which further suggested a causal relationship. Oppenheimer and Boitnott[18] reviewed the autopsy incidence of pancreatitis in 100 children with leukemia or nephrosis and found a 40% incidence of pancreatic lesions in nephrotic patients who received corticosteroids compared with a 14% incidence in controls. Three patients had acute hemorrhagic pancreatitis. There was a 16% incidence of pancreatic lesions in the children with leukemia, aplastic anemia, or tumors who had received corticosteroid or adrenocorticotropic hormone and no pancreatic lesions in the control group. The steroid dosage in these patients varied, but in some cases was as low as 15 mg/day of prednisone.[18] There is no correlation between the type of steroid, dosage, or duration of therapy and the incidence of pancreatitis.[19]

Fatty infiltration of the liver has been reported in adults. The fatty liver has been implicated as a source of fat emboli, which may be responsible for intestinal infarction or aseptic necrosis of bone in patients on steroid therapy.[20] Fatal fat embolism, thought to be secondary to corticosteroid therapy, has been reported in a 9-year-old child.[21]

MUSCULOSKELETAL COMPLICATIONS

The major musculoskeletal side effects of corticosteroid therapy include myopathy, osteoporosis, fractures, and avascular necrosis of bone.

Steroid myopathy usually develops insidiously. The weakness involves both upper and lower extremities, and

is more severe in the proximal musculature. Muscle wasting is also noted. There is a higher incidence of myopathy when using corticosteroids with a 9 α-fluoro configuration, such as triamcinolone or dexamethasone. However, steroid myopathy has also been reported in association with prednisone, prednisolone, and cortisone therapy. There is no relation between dosage or duration of therapy and the incidence of myopathy.[22] In a series of 250 patients with rheumatic fever who received corticosteroids, muscle weakness developed in five, which disappeared within two months when corticosteroids were discontinued. In two cases, weakness decreased when prednisone was substituted for dexamethasone.[23]

Osteoporosis occurs commonly in patients with endogenous Cushing's disease and is thought to be a common complication of steroid therapy. The catabolic effects of steroids, as well as the increased urinary excretion of calcium and decreased gastrointestinal absorption of calcium may all play roles in the development of osteoporosis. It is difficult to evaluate the role of steroids in osteoporosis because of inadequate quantitative criteria for the diagnosis of osteoporosis and insufficient knowledge of the spontaneous incidence of osteoporosis in association with various diseases.[14] Studies on the incidence of osteoporosis in children given steroids are lacking, but one of the complications of osteoporosis, vertebral collapse, has been reported in children.[24]

Osteoporosis has also been postulated as the cause of steroid associated avascular necrosis of the femoral head.[25] Fisher and Bickel,[20] however, have hypothesized that fat emboli in subchondral arterioles are responsible for this necrosis. Steroid associated aseptic necrosis has been reported in children suffering from asthma, rheumatoid disease, idiopathic thrombocytopenic purpura, and after renal transplantation.[25,26] In a series of ten transplant patients receiving corticosteroids, symptoms of aseptic necrosis appeared from two to ten months posttransplantation. Although the aseptic necrosis occurs most commonly in the femoral head, involvement of the knee and humeral head has also been reported.[25]

Recently, there have been case reports of acute arthralgia in adults secondary to large pulse doses of methylprednisolone. Some authors believe these arthralgias may be secondary to subtle avascular necrosis.[27]

RENAL COMPLICATIONS

The major renal complications of corticosteroids include nephrocalcinosis, nephrolithiasis, and uricosuria.

Kobayashi et al[28] in 1967, reported five cases of urinary lithiasis in steroid-treated children. They found increased urinary calcium excretion in these patients despite normal serum calcium levels. In a review of urinary tract calculi and nephrocalcinosis in pediatric patients by Daeschner et al,[29] both Cushing's syndrome and administration of corticosteroid were listed as predisposing factors for nephrocalcinosis and lithiasis.

ENDOCRINE AND METABOLIC COMPLICATIONS

Perhaps the most important complications of steroid therapy in children are the endocrine and metabolic disturbances, including growth failure, "steroid diabetes," hyperlipidemia, adrenal atrophy, hypocalcemia, hypokalemic alkalosis, and sodium retention with subsequent hypertension.[24]

Growth failure is perhaps the most important complication, but many studies on growth delay in steroid-treated children are difficult to interpret because the underlying disease for which the steroids are prescribed is usually associated with growth delay. It is particularly difficult to interpret studies on growth delay in which there is underlying endocrine disease: for example, hypopituitarism and congenital adrenal hyperplasia. In children receiving steroid therapy for nonendocrine disorders, questions regarding growth delay include: (1) What dose is necessary to suppress growth? (2) What is the potential for "catch-up growth" once steroids are discontinued? (3) What is the effect of alternate day therapy on growth? (4) What is the mechanism of this growth delay?

Kerrebijn and Kroon[30] studied the growth suppressive effects of steroids on asthmatic children ages 6 to 10 years who had no external signs of sexual maturity. They found that children receiving less than 3 mg/sq m/day of prednisone grew normally; those receiving more than 4 mg/sq m/day of prednisone had an increase in height of only 2 cm/yr, less than half of that expected for their age.[30]

In a study by Lam and Arneil[31] of nephrotic children, it was found that no child treated for less than three months had a change in the growth velocity, and although three of 14 children treated for less than six months had a decrease in their growth velocity during therapy, all had returned to their normal growth channel at follow-up five to ten years later. Among 16 children treated for longer than six months, 12 had a decrease in their growth velocity, and four of these had failed to return to their normal growth channel five to ten years after corticosteroids were stopped.

Studies by Morris[32] of asthmatic children suggested that the time needed for recovery from growth suppression may equal the time required for the development of the growth retardation. Thus, it seems that children treated for less than six months and with doses of less than 3 mg/sq m/day of prednisone do not suffer from substantial growth suppression. However, children treated for longer than six months may show a permanent decrease in growth channel and final adult height.

Asthmatic patients receiving alternate day prednisone may have substantially less growth delay than those on daily doses. Nephrotic patients receiving alternate day therapy also suffer less growth delay. In addition, Soyka[33] showed that children who had received daily steroid therapy often resumed normal growth when they were switched to alternate day therapy. Whether this increase in growth was related to the alternate day regimen or the decrease in total weekly dosage of corticosteroids is unknown.

Some of the mechanisms proposed to explain this steroid-induced growth

suppression include decreased growth hormone releasing hormone, decreased growth hormone, suppression of somatomedin synthesis or release, or an alteration in the somatomedin-active site in the cartilage cell. These first two theories have been disproved by Root et al[34] and Sadeghi-Nejad and Senior[35] who have shown that basal and insulin-stimulated growth hormone levels are normal in children on both daily and alternate day steroid regimens. Somatomedin suppression, however, may play an important role in growth retardation. Elders et al[36] have shown that plasma somatomedin activity decreases rapidly after an intravenous dose of methylprednisolone, and remains low during continuous therapy, but increases to normal when medication is omitted during the course of alternate day therapy. Studies on the somatomedin-active site in the cartilage have not yet been done.

Steroid diabetes is a well-known complication. It is characterized by insulin-resistance, hyperinsulinemia, rarity of ketosis, and near-normal fasting serum glucose levels despite a noticeably abnormal glucose tolerance test curves. The oral glucose tolerance test becomes more abnormal with increasing corticosteroid dosage. On low prednisone dosages, only the fasting and three-hour serum glucose levels are increased. As the prednisone dosage is increased, the mean fasting, one-hour, and three-hour serum glucose levels are all increased and the glucose tolerance test is similar to that of an insulin-dependent diabetic.[37] Although ketoacidosis is rare in steroid-induced diabetes, it has been reported in both children and adults.[38] In children with a positive family history for diabetes, a diabetic glucose tolerance test is more likely to develop while receiving steroids. Ruiz et al[39] found 15 cases of steroid-induced diabetes among 53 patients who had had renal transplants. Patients with a positive family history of diabetes had a higher incidence of this complication.

This steroid-induced diabetes may be an important factor in another metabolic side effect of steroid therapy, hyperlipidemia. Pennisi et al[40] recently reported hyperlipidemia in 18 of 27 children receiving steroids after renal transplantation. In this series, the serum cholesterol level increased with increasing steroid dosage, but was not related to the degree of obesity. Two patients were found to have decreased postheparin lipolytic activity and an abnormal accumulation of chylomicrons. The hyperlipidemia in these cases was reversed when steroid dosage was reduced.[40]

Abnormal fat accumulations are responsible for much of the classical "cushingoid" appearance of the child receiving steroids: the "buffalo" hump, truncal obesity, and the cherubic facies. Another less common complication of steroids is mediastinal lipomatosis. Roentgenographically, there is smooth symmetrical widening of the superior mediastinum. Price and Rigler[41] found eight cases of mediastinal lipomatosis among 97 renal transplant patients (ages 14 to 50 years) who had received corticosteroids. This complication developed in those patients who were receiving a higher mean daily prednisone dosage than in those patients who did not.

Perhaps, the most serious complication of steroid therapy is adrenal insufficiency after withdrawal of the drug. Adrenal atrophy probably does not occur in children receiving steroids for less than seven days.[24] The duration of adrenal insufficiency after cessation of steroid therapy is controversial. Graber et al[42] found that serum adrenocorticotropic hormone and cortisol levels did not return to normal after withdrawal of steroids or adrenocorticotropic hormone until nine months later. Aceto et al[43] studied the responses to metyrapone administration among 23 asthmatic children who had received glucocorticoids for long periods. They found a normal response to metyrapone in 70% of the children during the first month after glucocorticoid therapy had been discontinued. Two to six months after discontinuing glucocorticoids, 86% of the children had a normal response to metyrapone.

However, steroid-treated asthmatic children respond to hypoglycemic stress with a normal increase in plasma cortisol within two weeks of steroid withdrawal.[44] Responsiveness of the pituitary-adrenal axis is probably preserved to a greater degree in patients on alternate day therapy. Ackerman and Nolan[45] evaluated the adrenal response to hypoglycemia in ten adult nephrotic patients. They found that the plasma 17-hydroxycorticosteroid levels after hypoglycemia were normal in patients on alternate day therapy, but depressed in those receiving daily therapy. In any case, a child who has received steroids within the previous year should receive additional corticosteroids at times of severe stress, such as surgery.

Steroid Complications

- Ophthalmologic
  - Posterior subcapsular cataracts
  - Glaucoma
  - Reactivation of herpes keratitis
- CNS
  - Pseudotumor cerebri
  - Psychiatric disturbances and dependency
- Hematopoietic system
  - Leukocytosis, neutrophilia
  - Monocytopenia, lymphopenia, eosinopenia
  - Purpura
- Gastrointestinal system
  - Pancreatitis
  - Peptic ulcer
  - Fatty infiltration of the liver
- Renal system
  - Nephrocalcinosis
  - Nephrolithiasis
  - Uricosuria
- Musculoskeletal system
  - Myopathy
  - Osteoporosis and fractures
  - Aseptic necrosis of bone
- Endocrine and metabolic
  - Diabetes
  - Adrenal insufficiency
  - Growth failure
  - Hyperlipidemia
  - Lipomatosis
  - Hypocalcemia
  - Hypokalemic alkalosis
  - Sodium retention and hypertension

IMMUNOLOGIC COMPLICATIONS

The anti-inflammatory and immunosuppressive effects of steroids are well known. A detailed discussion of these effects is beyond the scope of this review. Many reports of secondary and opportunistic infections in children receiving steroid therapy have been published. Steroids are thought to depress the immune response in the following ways: (1) interfering with phagocytosis and intracellular digestion; (2) inhibiting migration of cells to areas of inflam-

mation; (3) reducing humoral antibody titers; and (4) suppressing cell-mediated hypersensitivity.[46]

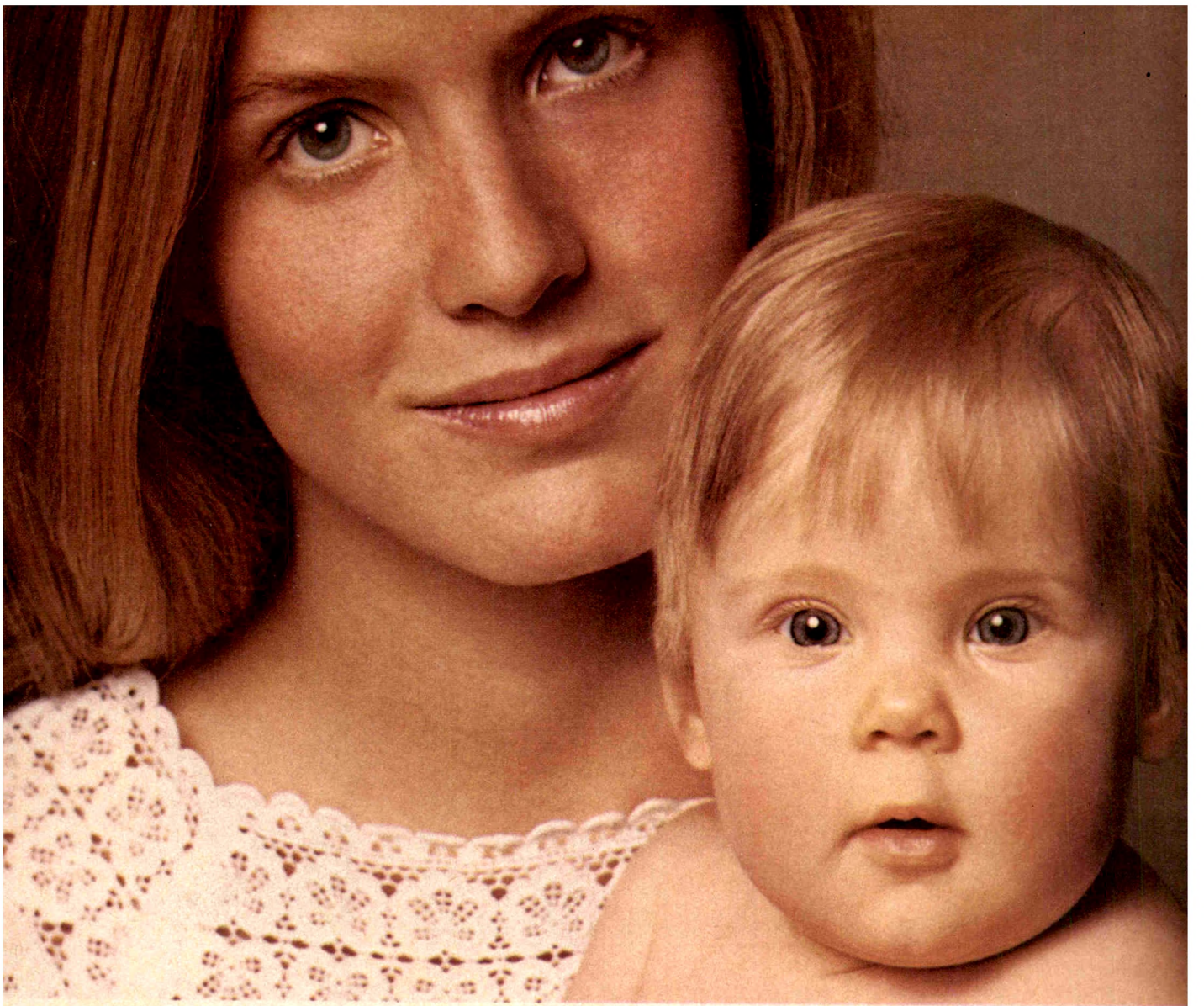
These immunosuppressive effects are probably less severe in patients receiving alternate day therapy. MacGregor et al[47] showed that delayed hypersensitivity responses to appropriate antigens increased in seven patients when they were switched from a daily to an alternate day prednisone regimen. Dale et al[13] showed that cutaneous inflammatory responses were decreased in patients receiving daily steroids, but in patients receiving alternate day therapy, the inflammatory responses were normal on the "off" day. The monocytic inflammatory response was decreased in patients on alternate day therapy on the "on" day.[13]

FETAL AND NEONATAL COMPLICATIONS

Recent interest in glucocorticoid prophylaxis for respiratory distress syndrome has stimulated further study of the toxic effects of steroids on the fetus and the neonate. This subject has recently been reviewed by Tauesch[48] and will not be discussed here in detail. Tauesch concluded, however, that "no examples of fetal or maternal risk have been documented to date in human beings that would obviate the potential benefit of this form of (steroid) therapy."

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[1] Material presented at March 23, 1977, symposium, Infant Nutrition: A Foundation for Lasting Health?



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Radiological Case of the Month

Lionel W. Young, MD; Contributed by James E. Crowe, MD, Thomas E. Sumner, MD

Clinical History.—A newborn infant boy had respiratory distress that began immediately after birth.

From the Department of Radiology, Bowman Gray School of Medicine, Winston-Salem, NC.
Reprint requests to Department of Radiology, Children's Hospital of Pittsburgh, 125 DeSoto St, Pittsburgh, PA 15213 (Dr Young).

Physical Examination.—He weighed 1,910 g, was tachypneic, with intercostal retractions and grunting, and had a slightly scaphoid abdomen. Combined chest and abdominal roentgenograms were obtained (Fig 1 and 2).

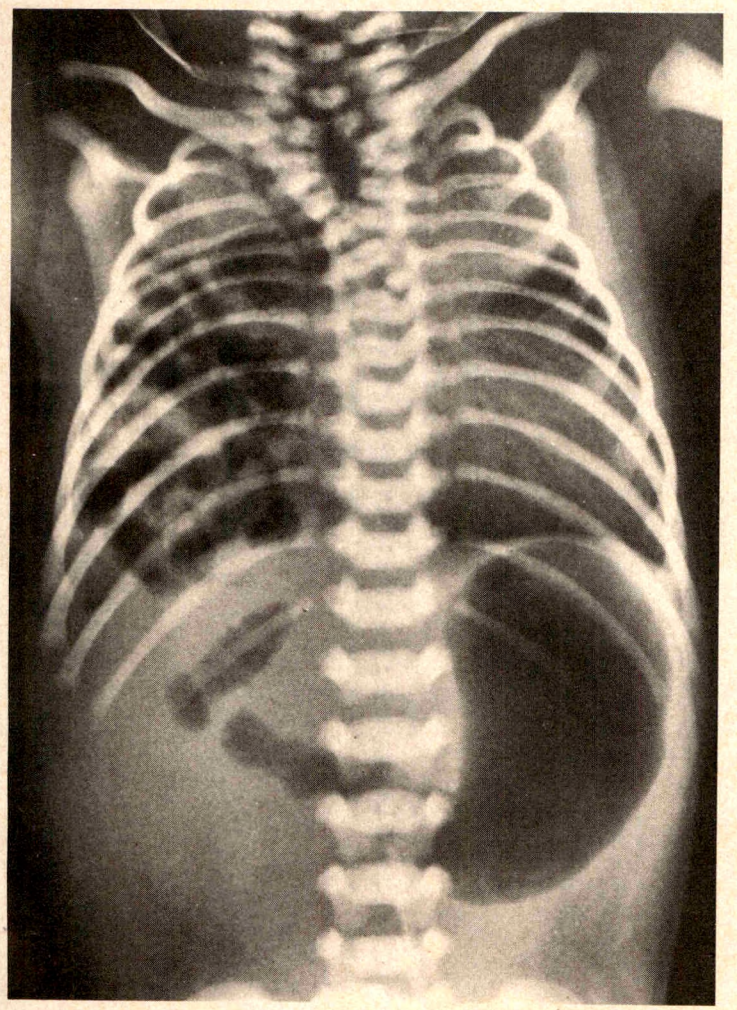


Fig 1.

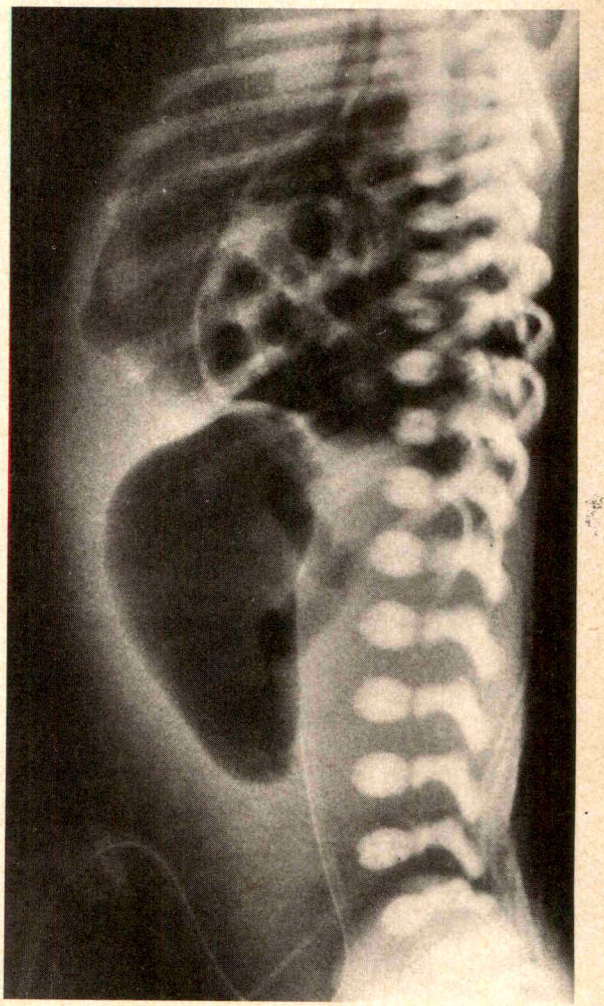


Fig 2.

Denouement and Discussion

Fig 1.—Anteroposterior view of chest and abdomen showing anomalies of lower cervical and upper thoracic spine characterized by cleft in vertebrae. Appearance of right side of chest is consistent with numerous gas-filled loops of bowel within it.

Fig 2.—Lateral view is consistent with herniation of bowel through posterior aspect of diaphragm (Bochdalek hernia).

Split Notochord Syndrome

The vertebral anomalies of anterior and posterior spina bifida are often accompanied by a characteristic complex of visceral and neural abnormalities. One of the embryologic explanations for this combination of anterior and posterior spina bifida is the "split notochord" theory. This theory proposes that a primitive node cell rest persists in the midline, producing a notochordal cleft that causes the vertebral centra to be laid down in independent halves.[1]

The most common visceral anomalies present in infants and children with the split notochord syndrome are mediastinal cysts of foregut origin (neurenteric cysts) and enteric duplications, most of which arise from the small intestine. On occasion, a large diaphragmatic hernia is present, as in this case. In some cases, a cystic duplication arises from the small intestine, passes through a defect in the diaphragm, and is seen clinically and roentgenographically as a mediastinal mass.

In the case presented in this article, a posterior mediastinal cyst was present on the right side but was obscured on the roentgenogram by herniated bowel. At surgery for repair of the Bochdalek hernia, reduplication of the bowel with malrotation was also noted. The duplicated bowel was resected. After a stormy course with difficulty in oxygenation, the patient had acute respiratory failure and died.

Meningomyeloceles and severe developmental anomalies of the hind brain and cervical spinal cord may also occur and may make for a poor prognosis. Rarely, the bowel may pass through the spinal cleft and appear on the back (dorsal enteric fistula), usually in association with meningomyelocele and imperforate anus.[2]

Although the vertebral anomalies in this case are grossly evident, mediastinal cysts and duplications are more often accompanied by relatively minor spinal anomalies, some of which can only be demonstrated by special roentgenographic techniques, such as tomography.

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The Editors welcome contributions to "Picture of the Month" and "Radiological Case of the Month." Those who wish to contribute should send their manuscripts to Dr Gellis (Picture of the Month), Boston Floating Hospital, 20 Ash St, Boston, MA 02111, or Dr Young (Radiological Case of the Month), Department of Radiology, Children's Hospital of Pittsburgh, 125 DeSoto St, Pittsburgh, PA 15213. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.

Stapedial Hypoplasia in Partial DiGeorge's Syndrome

DiGeorge's syndrome applies to immunodeficiency associated with abnormal development of the third and fourth pharyngeal pouches.[1] Cardiac[2] and facial maldevelopment[3] not directly related to the third and fourth pouches may be associated with the syndrome, and incomplete variants have been recognized.[4] Middle ear structures that derive from branchial anlage are not readily accessible for clinical study and are rarely commented on in descriptions of the DiGeorge's syndrome. We describe an infant with partial DiGeorge's syndrome in whom middle ear derivatives of the second branchial arch were hypoplastic.

Report of a Case.—A 2,800-g boy was born to a 19-year-old gravida 1, para 0 after a 40-week gestation. At 30 hours, cyanosis and respiratory distress developed that was associated with absent peripheral pulses and a grade 2/6 murmur at the left sternal border. Roentgenograms showed an enlarged heart, increased pulmonary vascular markings, deformed T-10 with bilateral hemivertebrae, and synostosis of the right eighth and ninth and left tenth and 11th ribs. Cardiac catheterization showed a severe periductal coarctation. The infant died at 48 hours during attempted repair of the coarctation. Laboratory values were as follows: WBC, 13,500/cu mm, with 40% segmented neutrophils, 1% band forms, 46% lymphocytes, and 9% monocytes; and serum calcium, 8.5 mg/dl.

Postmortem examination showed no external maldevelopment. There were severe preductal aortic coarctation, hypoplasia of the aortic isthmus, and an intracristal ventricular septal defect, with absent conal papillary muscle. The ductus arteriosus was widely patent and the aortic valve bicuspid. Nonfused thymic lobes with a combined weight of 5 g were present in the lower neck. The thymus was microscopically normal without involution. Serial sections through the thyroid and paratracheal tissues from the larynx to the carina disclosed a single parathyroid gland 550 μ in greatest diameter adjacent to the thymus. The peripheral lymphoid tissues were unremarkable.

Temporal bones were removed with an oscillating bone plug saw. Both stapes had a small head with a normal anterior crus extending to the footplate. The stapedius tendon was present and attached to the lower portion of the stapedial head. The posterior crus was rudimentary and did not reach the footplate (Fig 1). Both stapes were mobile, but the footplates were irregularly shaped and approximately one third normal size. The oval windows were correspondingly malformed and reduced in size (Fig 2). The upper elements of the ossicular chain, including the lenticular process of the incus and incudostapedial articulation were normal as were the semicircular canals, otolith organs, and cochleae.

Comment.—An association between congenital anomalies of the thymus, parathyroid glands, great arteries, and related structures has been known for many years. The recognition by DiGeorge that immune deficiency may result from the thymic abnormality has prompted considerable recent interest.

Lischner[5] suggested that DiGeorge's syndrome be applied only to those cases with thymic agenesis proved by postmortem examination

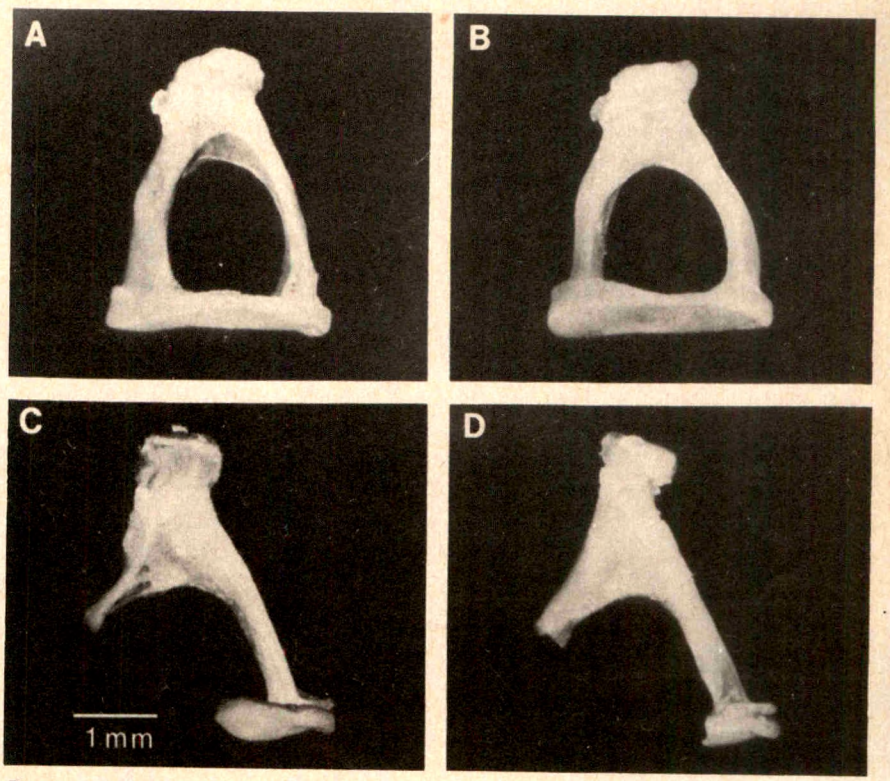


Fig 1.—Normal left and right stapes from 1-week-old infant (A and B). Deformed, hypoplastic left and right stapes from present case (C and D).

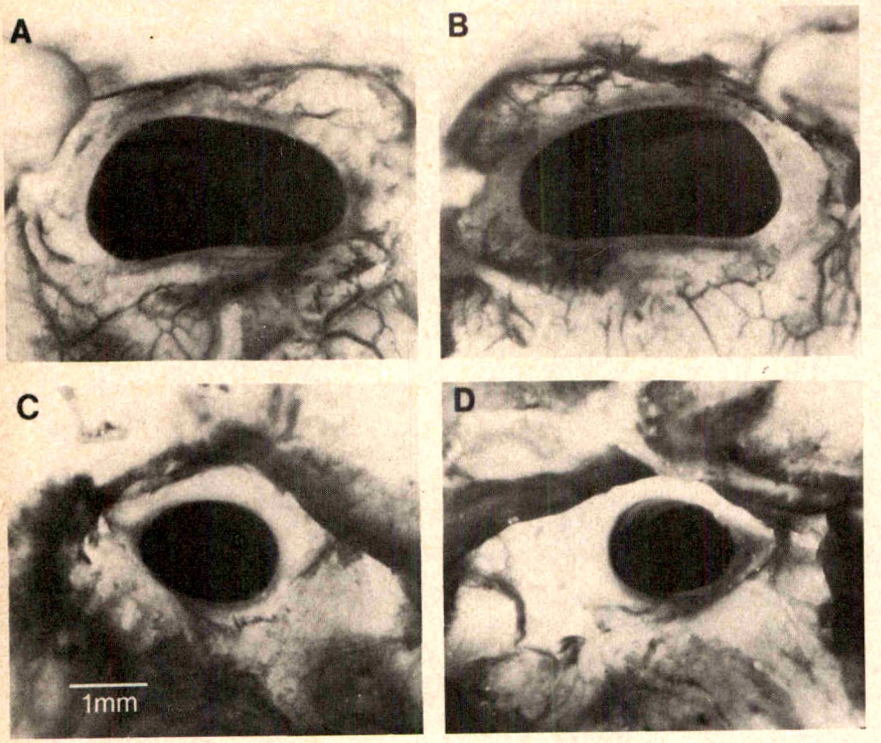


Fig 2.—Normal left and right oval windows from 4-day-old infant (A and B). Malformed left and right oval windows from present case (C and D).

and that partial DiGeorge's syndrome be applied to cases showing thymic hypoplasia. Regardless of terminology, it is clear that the defect frequently involves structures beyond those derived from the third and fourth pharyngeal pouches. Patients may have cardiac defects related to conotruncal maldevelopment, facial anomalies, and thyroid hypoplasia. It is difficult to envision an isolated malformation that could produce defects in all of these structures. A generalized insult to branchial development seems more likely.

Crura of the stapes are derived from mesenchyme of the second branchial arch.[6] Isolated absence of a stapedial crus is found at surgery with extreme rarity.[7] We consider that maldevelopment of the crura in the present case was related to a more generalized defect of branchial morphogenesis as a component of the partial DiGeorge's syndrome. Although abnormalities of the external ear have been noted in DiGeorge's syndrome, associated maldevelopment of middle ear structures has only rarely been mentioned. Kretschmer et al[3] noted anomalous middle ear development in one affected infant. Miller et al[8] found one middle ear defect in a review of 156 patients with idiopathic hypoparathyroidism. The absence of descriptions of middle ear anomalies in DiGeorge's syndrome is probably not a reflection of their rarity but of the difficulty in making relevant observations. The middle ear is not accessible to routine clinical examination nor are anomalies of the stapes, as encountered in the present case, likely to be recognized by gross hearing loss. Examination of the middle ear ossicles is not a part of the routine postmortem examination; our observations were incidental to an unrelated study.

Our case shows that maldevelopment of second branchial arch derivation may accompany the more commonly encountered anomalies of the third and fourth pharyngeal pouches.

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This research was supported in part by a grant from the Leland Fikes Foundation.

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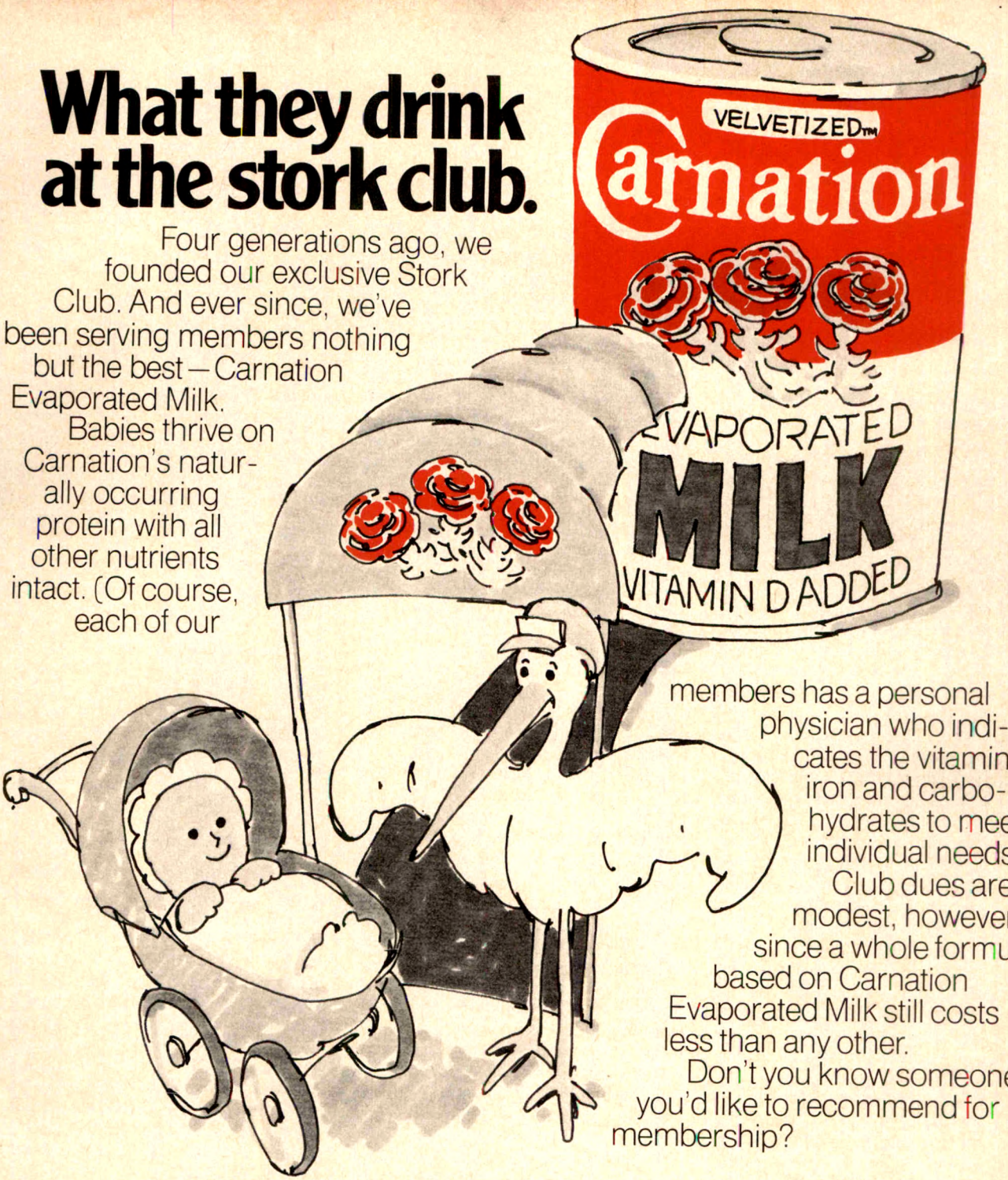
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Letters to the Editor

Goldenhar Syndrome and Airway Management

Sir.—As an anesthesiologist who has had experience with three children with Goldenhar syndrome, I read with interest the article by Feingold and Baum in the February JOURNAL (132:136-138, 1978). Whenever such a child is to be admitted for surgery, the anesthesiologist should be notified in advance since these children may be difficult (or impossible) to intubate. I suggest the following procedure: (1) Explain to the parents that a tracheotomy may be necessary, and obtain consent. (2) Have an experienced otorhinolaryngologist present during introduction who is gowned and gloved, with a tracheotomy set open and ready. (3) Induce anesthesia with a potent inhalation anesthetic (halothane or enflurane) and oxygen, thus omitting nitrous oxide to provide a high inspired oxygen concentration and avoid fixed agents, permitting the child to maintain his own airway. (4) Laryngoscope the patient under deep anesthesia without the aid of muscle relaxants. (5) If the vocal cords cannot be visualized, attempt blind intubation (nasally or orally). (6) If intubation is not possible, do not continue to traumatize the child—proceed with tracheotomy if it is inappropriate to maintain anesthesia by a mask.

The child's external appearance is not a reliable guide to potential airway problems. Mandibular hypoplasia, facial asymmetry, and micrognathia are evident. However, limitation of neck movement resulting from vertebral anomalies is most important.

These children often require multiple procedures, and previous anesthetic records should be consulted. Each of the author's patients required three anesthetics and the anesthetic course was consistent: one child required tracheotomy each time; one was moderately difficult to intubate; and the third was intubated with ease each time.

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Agammaglobulinemia

Sir.—Pick et al in their interesting article in the JOURNAL (131:682-686, 1977) described a case of agammaglobulinemia characterized by the absence of IgG, IgA, IgD, and the salivary "secretory component" associated with a plasma cell dyscrasia and amyloidosis. They include a summary of the findings in other cases of amyloidosis associated with agammaglobulinemia.

One report that they did not include was relevant to the subject. I refer to the article by Ziegler and Penny[1] in which they described the first reported case of X-linked hypogammaglobulinemia associated with amyloidosis. The patient, a 14-year-old boy, died of meningoencephalitis and its sequelae, and at autopsy amyloid was detected in the liver, thymus, tonsils, and kidney.

I would also like to correct an inaccuracy in the comment by Pick et al. They state that seven of ten cases discussed by Mawas et al[2] seem to have a "mixed pattern" of amyloid deposition and that this supports their theory that this is the predominant pattern of amyloid deposition in agammaglobulinemia. In fact, Mawas et al reviewed only six cases, not ten. The mixed pattern theory, ie, mixed primary and secondary amyloidosis, may well be true, but incorrect evidence should not be used in its support. The detection and analysis of amyloid in larger numbers of patients with agammaglobulinemia will hopefully clarify this point.

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Dr Pick declined to reply.—ED.

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Wolfram Syndrome

Sir.—We read with great interest the report by Carson et al on simultaneous occurrence of diabetes mellitus, diabetes insipidus, and optic atrophy in a brother and sister (*Am J Dis Child* 131:1382-1385, 1977) and would like to add the following data that seemed to have escaped the attention of the authors. A review of 91 cases with this syndrome called Wolfram syndrome has been published by Cremers et al.[1] These authors also report a postmortem on one patient that disclosed noticeable dilation of the renal pelvis, ureters, and bladder. The hypophysis, hypothalamus, thalamus, substantia nigra, and red nucleus were normal. The optic nerve, chiasma, and both optic tracts showed slight gliosis and a loss of myelin structure, but no signs of active myelination.

From this clinic, we have reported in 1975,[2] two brothers with juvenile diabetes mellitus and optic atrophy with hypothalamic disease as judged by clinical findings. In one brother, bilateral hydronephrosis and hypo-

tonic bladder were demonstrated. Both died at age 17 and 21 years, respectively. On the older brother, an autopsy was performed and the main findings were as follows: severe atrophy of the whole optic tract; loss of neurons in the hypothalamic nuclei; accumulation of iron and calcium in the hypothalamic nuclei; and severe atrophy of the pons. The full report of the neuropathological findings has been prepared for publication.

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Incorrect Use of χ^2

To the Editor.—An article by Weston et al (*Am J Dis Child* 131:1241-1242, 1977) exemplifies a continuing misuse of χ^2 methodology in the literature. This is the use of χ^2 to compare things other than the number of "successes" in N trials.[1(p43)]

For the χ^2 method to be proper, the mean percent of cells responding would have to include the total number of cells used in each group. What the authors wanted to do was compare two groups of data that just happened to be percent cells responding for each subject.

The most appropriate method of analysis would have been the Mann-Whitney U test.[1(p109)] The usual t test could have been used but it would have required an arc sine transformation of each value,[1(p185)] a tedious problem.

Weston et al found no substantial difference between newborns and controls for monocyte phagocytosis and bactericidal activity. Using the summary statistics provided, I performed a t test for these two comparisons, recognizing that the method would only be approximately correct. I found $P < .05$ for the former and $P < .001$ for the latter.

The authors should rerun those comparisons with the Mann-Whitney test to obtain a more correct comparison.

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Infectious Mononucleosis

Sir.—I would like to mention an additional clinical feature of infectious mononucleosis not included by Drs Rapp and Hewetson in their comprehensive review article in the JOURNAL (132:78-85, 1978). In 1967, Pullen et al[1] first noted the high incidence (95%) of maculopapular rashes in patients with mononucleosis who received ampicillin. This observation in adult patients was corroborated in children by a retrospective multicenter study[2] that showed that the characteristic exanthem developed in all 13 patients with infectious mononucleosis who received ampicillin.

Typically, the rash begins five to ten days after beginning ampicillin therapy. Macules and papules appear first on the trunk and after three to four days, the rash becomes generalized. Pruritus is freuqently present and is often severe. This exanthem usually persists for several days and sometimes resolves with desquamation.

This high incidence (69[3]–100%) of morbiliform eruptions contrasts sharply with the natural presentation of rashes in infectious mononucleosis. As Drs Rapp and Hewetson pointed out exanthems develop in only 3% of all patients with infectious mononucleosis. Shapiro et al[4] and Kerns et al[5] report an incidence of ampicillin-related rashes in the general adult and pediatric populations of 9.5%.

The causal mechanism of the ampicillin-related rashes and an explanation for this increased incidence in infectious mononucleosis are not yet known. It is important, however, for the clinician to note this association. One should avoid using ampicillin in a patient with possible infectious mononucleosis and consider the diagnosis of infectious mononucleosis with ampicillin-related rashes.

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Adverse Reactions to Food Can Cause Hyperkinesis

Sir.—Recently, Dr Esther H. Wender discussed the controversy over the relationship of diet to hyperkinesis in children (*Am J Dis Child* 131:1204-1206, 1977). As she indicated, several recent studies have failed to document the Feingold thesis that food additives and salicylates play a major role in causing this disorder.

Yet, despite these negative results, an increasing number of observers report that hyperactive behavior can be modified by dietary manipulation. And a congressional committee and the media have given wide publicity to this point of view (*Wall Street Journal*, June 2, 1977, p 1; "MacNeil-Lehrer Report," Public Broadcasting System, June 22, 1977; "CBS Evening News," CBS Inc, June 22, 1977).

Moreover, the relationship of food sensitivity to systemic and nervous system symptoms in children has been described by numerous observers during the past 50 years.[1-9]

Nevertheless, many physicians remain skeptical—even hostile—to the concept that diet can affect behavior. A typical response is, "These reports are based on testimonial data. They are 'unscientific' and unsubstantiated. And before I put a hyperactive child on an elimination diet, someone will have to prove such a diet works and *explain the mechanisms involved.*"

Certainly I can understand why physicians are reluctant to embrace any therapy that lacks scientific docu-

mentation. But when the therapy is safe (as in the case of a trial elimination diet), such reluctance may not be in the best interest of the patient.

Why has the relationship of diet to hyperactivity been so hard to prove and so slow in forthcoming? In my opinion, the major cause for the confusion and delay has been improper design of the research studies.

Because Dr Feingold placed the blame for hyperactivity solely on food colors, dyes, additives, and salicylates, most studies, to prove or disprove the Feingold thesis, have eliminated *only* those substances from the diet. And because the children continued to consume a number of foods that cause adverse reactions, their behavior showed little or no change. So several studies have had "negative" or equivocal results.

In my practice, for the past five years I've seen more than 160 "new patients" with hyperactivity. And using elimination diets, I found the hyperactivity diminished in more than 75% of these children. Sugar and milk led the list of foods causing hyperactivity. Yet, eggs, corn, wheat, citrus, beef, pork, and other "everyday foods" were troublemakers in many of my patients. Although some children showed nervous system reactions after the ingestion of food colors and dyes, many more reacted to the foods themselves.

In studying these patients, I found that most of their conditions improved substantially—even dramatically—when offending foods were avoided for seven days. The effect of the foods on the child's behavior was confirmed by returning the foods to the child's diet, one at a time, beginning on the eighth day.

I freely admit that the conditions of some of my patients who were hyperactive may have improved after dietary manipulation for a variety of reasons (including coincidental, psychological, and nutritional reasons). And I make no claim to understand the mechanisms involved. Yet I know, beyond any shadow of a doubt, based on what parents of my patients tell me, that many, and perhaps most, hyperactive children can be helped by changing their diets.

Perhaps "scientific proof" of the relationship of diet to hyperactivity will soon be established. But until such time, I urge skeptics to suggest carefully planned elimination diets for their patients who are hyperactive. I'll be happy to send a copy of the diet I use to anyone who requests it. (Please enclose a stamped, self-addressed envelope.)

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In Reply.—Dr Crook's comments get right to the heart of the issues involved in the relationship between diet and behavior. He says, "I freely admit that the conditions of some of my patients who were hyperactive may have improved after dietary manipulation for a variety of reasons. . . . , I make no claim to understand the mechanisms involved." The point is that Dr Feingold *does* make a claim that the mechanism underlying behavioral change is the body's response to specific food additives. I agree that there is apparently a relationship between diet and behavior. (Dr Conner's studies demonstrate this, for example.) What isn't clear is whether behavioral change is attributable to food additives or other effects such as psychological ones. For the practitioner whose main goal is to improve function, it may not matter whether improvement is a result of one factor or another, as long as the treatment is not harmful. But questions of public policy must not be decided without careful study of "the mechanisms involved."

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Contraindications: Hypersensitivity to sulfonamides; infants less than 2 months of age; pregnancy at term and during the nursing period.

Warnings: Safety in pregnancy not established. Do not use for Group A beta-hemolytic streptococcal infections, as sequelae (rheumatic fever, glomerulonephritis) are not prevented. Deaths reported from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias. Sore throat, fever, pallor, purpura or jaundice may be early indications of serious blood disorders. CBC and urinalysis with careful microscopic examination should be performed frequently.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy or bronchial asthma. Hemolysis, frequently dose-related, may occur in glucose-6-phosphate dehydrogenase-deficient patients. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias:* Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia; *Allergic reactions:* Erythema multiforme (Stevens-Johnson syndrome), generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis; *Gastrointestinal reactions:* Nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis; *C.N.S. reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia; *Miscellaneous reactions:* Drug fever, chills and toxic nephrosis with oliguria and anuria. Periarteritis nodosa and L.E. phenomenon have occurred. Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia as well as thyroid malignancies in rats following long-term administration. Cross-sensitivity with these agents may exist.

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Contraindications: Hypersensitivity to trimethoprim or sulfonamides. Pregnancy and during the nursing period. Infants less than two months of age.

Warnings: SEPTRA SHOULD NOT BE USED IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS.

Clinical studies have documented that patients with Group A β-hemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with Septra than do those patients treated with penicillin as evidenced by failure to eradicate this organism from the tonsillopharyngeal area.

Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias. Experience with trimethoprim alone is much more limited, but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides.

Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBCs are recommended; therapy should be discontinued if a significant reduction in the count of any formed blood element is noted.

Precautions: Use with caution in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur (frequently dose-related). During therapy, maintain adequate fluid intake and perform frequent urinalyses with careful microscopic examination and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Septra. *Blood Dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic Reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal Reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *C.N.S. Reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous Reactions:* Drug fever, chills, and toxic nephrosis with oliguria and anuria. Periarteritis nodosa and L.E. phenomenon have occurred. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia; cross-sensitivity may exist with these agents. In rats, long-term administration of sulfonamides has produced thyroid malignancies.

Dosage and Administration: Not recommended for use in infants less than two months of age.

ACUTE OTITIS MEDIA IN CHILDREN: The recommended dose for children with acute otitis media is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, given in two divided doses every 12 hours for 10 days. The following table is a guideline for the attainment of this dosage using Septra Tablets or Suspension.

Children: Two months of age or older:

Weight		Dose—every 12 hours	
lb	kg	Teaspoonfuls	Tablets
20	9	1 (5 ml)	½
40	18	2 (10 ml)	1
60	27	3 (15 ml)	1½
80	36	4 (20 ml)	2 (or 1 DS tablet)

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual Standard Regimen
15–30	Half of the usual dosage regimen
Below 15	Use Not Recommended

Supplied: SEPTRA TABLETS containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 40, 100, 500 and 1000 tablets; unit dose pack of 100. ORAL SUSPENSION, containing the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole in each teaspoonful (5 ml), cherry flavored—bottle of 450 ml.

Also available in double strength, oval-shaped, pink, scored tablets containing 160 mg trimethoprim and 800 mg sulfamethoxazole—bottles of 60 and unit dose packs of 100.

*Clinical results do not necessarily correspond with *in vitro* data.

†Data on file, Medical Department, Burroughs Wellcome Co.

Wellcome
Burroughs Wellcome Co.
Research Triangle Park
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Books

Infectious Diseases of the Fetus, edited by Jack S. Remington and Jerome O. Klein, $45, 1,121 pp, Philadelphia, WB Saunders Co, 1976.

Infectious diseases remain an important problem in neonatal and perinatal medicine. This text, edited by Drs Remington and Klein, with chapters by a distinguished group of contributors, is an extremely thorough review of the current state of the art. Containing 1,121 pages, the volume covers most microorganisms that have the capacity to produce disease in the newborn, at least in the Western world. General chapters on immunology and resistance to infection and clinical pharmacology of antibacterial agents are included along with the specific infectious disease topics. The depth of coverage of the material is indicated by the fact that the book is longer than any existing text covering all of pediatric infectious diseases. This, unfortunately, is a reflection on the lack of a comprehensive text on pediatric infectious diseases rather than on this volume by Drs Remington and Klein.

In general, the editors and authors have done a remarkable job of achieving their objective, "to provide a complete, critical and comprehensive review...." The bibliographies with each chapter are exhaustive and provide the reader with an excellent reference resource. The chapter on toxoplasmosis, for example, contains more than 600 references. Illustrations and tables are ample and in general, highlight important information. In spite of its length, this is a very readable volume although there are some differences in style and in detail. The chapter on hepatitis, for example, is 28 pages whereas the coverage of toxoplasmosis covers 142 pages. Some chapters insert references within the text, whereas others are collected at the end of the chapter. Some chapters, for example, the one on listeriosis, includes more experimental data and other information that is less directly related to management of the neonate. If there is a problem it may be that some topics are presented in such detail that the casual reader may not be sufficiently diligent to cover the material presented, although I would certainly hope that that is not the case.

This text is a valuable addition to the literature and extremely up to date for a volume of its length. It is recommended for medical and pediatric department libraries, for those interested in neonatal and perinatal medicine, for pediatricians or obstetricians with a subspecialty orientation in infectious diseases, and as a reference source for pediatricians, family practitioners, obstetricians, and medical students.

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Haven in a Heartless World, by Christopher Lasch, $10, 230 pp, New York, Basic Books Inc, 1977.

Haven in a Heartless World presents the thesis that the emergence of capitalism created in the 18th and 19th centuries, "the bourgeois family system"; a system in which marriage took place at a relatively late age (compared to other societies) and was arranged by the individuals involved, not by their families. Children came to be seen not as little adults but as people with distinct attributes, "impressionability, vulnerability, innocence, which required a warm, protected, and prolonged period of nurture." As a result, child rearing became more demanding and emotional ties between parents and children more intense. The nuclear family, with increasingly attenuated ties to an extended kin network, became "an emotional refuge in a cold and competitive society...." "Yet the very conditions that gave rise to the need to view privacy and the family as a refuge from the larger world made it more and more difficult for the family to serve in that capacity."

It is Lasch's contention that what has made this new family form unable in the 20th century to provide refuge was "the intervention of planners and policy-makers," leading to the proletarianization of parenthood. In essence, service providers of all sorts in the first three decades of the present century intruded into the family in an attempt to "Americanize" the children of immigrants: "Reformers sought to remove children from the influence of their families, which they also blamed for exploiting child labor, and to place the young under the benign influence of state and school." This undermined the family's ability to provide for itself and thereby justified the continuing expansion of health, education, and welfare services.

Much of the ideological underpinning of this movement was provided by the emerging fields of sociology, anthropology (particularly the culture and personality school), and psychiatry. All these fields had in common a revision-or neglect-of Freud's insights regarding the irreconcilable conflict between the individual and society, essentially an oversocialized view of man. According to Lasch, the intrusion of experts into the family (through schools, training manuals, social workers, and a myriad of other ways) has attenuated the bonds between parents and children. In addition, with fathers retreating into the workplace and with parents possessing skills that rapidly become obsolete and therefore cannot be passed on to their children, children are unable to resolve their Oedipal conflicts with a more realistic assessment of their parents. The child remains at a narcissistic stage: he "no longer wishes to succeed the father. Instead, he wishes merely to enjoy life without his interference—without the interference of any authorities at all." This serves the needs of the advanced capitalistic society by encouraging high levels of consumption.

This thesis raises several questions that can only be touched on in a brief review. First, as Davis[1] has pointed out, "Lasch's theory... overlooks the misery, shame, violence, humiliation, and ignorance of the 'premodern' family." Although this may be an overdrawn description of premodern families, there is in Lasch's account an assumption that family life was better at some time in the past than it is now.

Second, there is no account of how the so-called helping services and the academic fields emerged that provided their intellectual and ideological underpinnings. What were their institutional bases? Who entered such fields? And what were the objective social conditions with which they were confronted and to which they were reacting?

Third, it is not clear how much influence such service providers actually have had. Nor is it clear which way the causal connection, if there is one, operates. Did social services emerge to deal with real problems that real people were having or did they only emerge to serve the needs of the service providers and the new

industrial order of which they were representatives? Lasch asserts the latter is the case, but provides no empirical evidence to demonstrate it. Undoubtedly, service professions have been self-serving to a considerable degree, but the conditions that led to their emergence at the turn of the century, squalid living conditions in the urban slums, for instance, were real and are not even mentioned.

Fourth, there evidently was a transition at some point from a concern with Americanizing immigrants to processing the middle class. Lasch in passing indirectly alludes to this issue. It also seems, for example, that the people who read various child rearing manuals belong to the middle class. The relatively few lower class families who also read them use them as guide books for upward social mobility.[2] Yet Lasch treats American families alike, again without empirical data for support. Nowhere is the issue of the service providers' clientele seriously and directly discussed.

Finally, there may be other sources of change in the pattern of relationships within the nuclear family than those created by imperialistic service professions. For example, kinship networks in urban families have been found in many cases to be much stronger than Lasch allows, and this in turn seems to be related to patterns of conjugal relationships and child rearing practices.[3] Moreover, the influence of the workplace on the values in the home are not mentioned but may have importance: people with relative autonomy at work (primarily the middle class) seem to value independence and autonomy in their children, whereas those working in authoritarian situations such as factory workers (primarily of lower social class) seem to value conformity.[2]

Having said this, however, it must also be pointed out that service professions do tend to redefine their missions in ways that lead to their continued growth and well-being. We may take the increasing interest in a redefinition of primary care pediatrics as an example. In conscious response to a declining birth rate, the care of complicated medical cases by subspecialists, and a variety of other factors, Pless[4] suggests a number of "areas into which primary care could expand": community involvement, health education, preventive pediatrics, behavioral problems, and social problems. Characteristically, it is the academic leaders of a profession (in this case pediatrics) rather than the rank-and-file who are the ones calling for such a redefinition and expansion. It is by no means clear that the current generation of practitioners would be sympathetic to such a change, but through their influence within the professional schools academic leaders are probably able to effect a gradual change in the attitudes of their students and hence in future generations of practitioners. As noted previously, it is uncertain what the consequences of these changes are, particularly as other elements of the social structure are simultaneously influencing family life. Nonetheless, Pless's epigrammatic quotation from George Bernard Shaw appears apposite: "Every profession is a conspiracy against the laity."

Lasch's book is undeniably stimulating and provocative. It fails to deal adequately with a number of substantial issues, some of which have been noted already; it perhaps places too much responsibility on service professions for adversely influencing family life, certainly no empirical evidence is provided from which one could draw these conclusions; it assumes but does not demonstrate a continuous decline in the quality of family life; and it seems to imply that the malign influence of the helping professions has been the result of a conscious plot to destroy family ties and therefore make individuals increasingly susceptible to the manipulation of the economic order and the state. But, like Ivan Ilich, Lasch has raised serious and valid questions about the beneficence of the helping services. As the service sector is the most rapidly growing part of the nation's economy, such questions will become ever more pressing.

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**"Lacking substantial evidence of effectiveness as a fixed combination": For the prophylaxis and treatment of the symptoms associated with the common cold.
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American Journal of Diseases of Children

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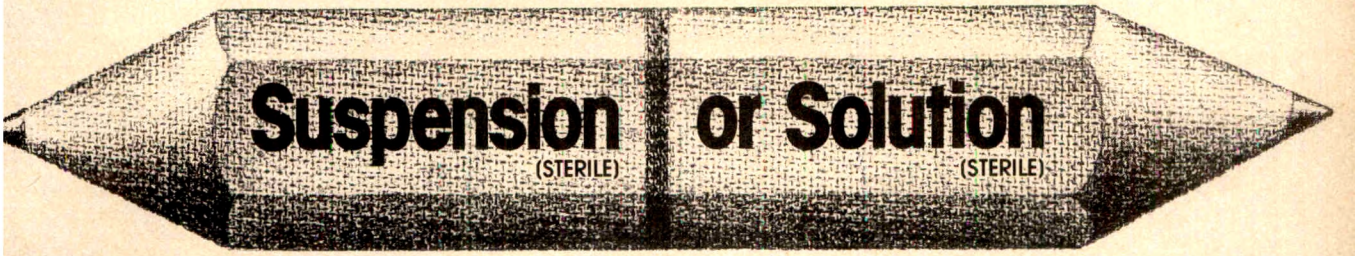
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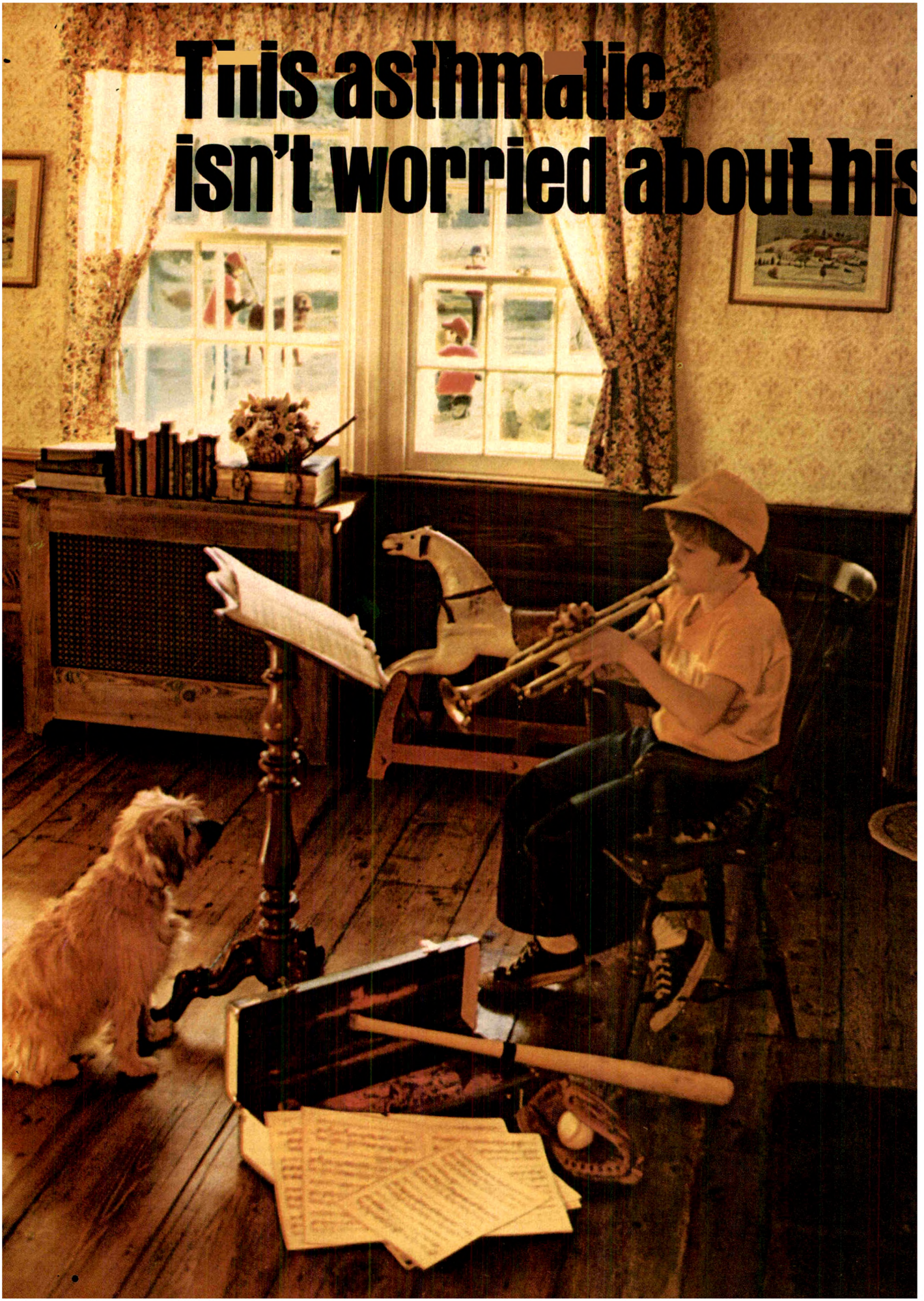
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Precautions: Use with caution in patients with cardiac disease, hepatic or renal impairment. Concurrent administration with certain antibiotics, i.e. clindamycin, erythromycin, troleandomycin, may result in higher serum levels of theophylline. Plasma prothrombin and factor V may increase, but any clinical effect is likely to be small. Metabolites of guaifenesin may contribute to increased urinary 5-hydroxyindoleacetic acid readings, when determined with nitrosonaphtol reagent. Safe use in pregnancy has not been established. Use in case of pregnancy only when clearly needed.

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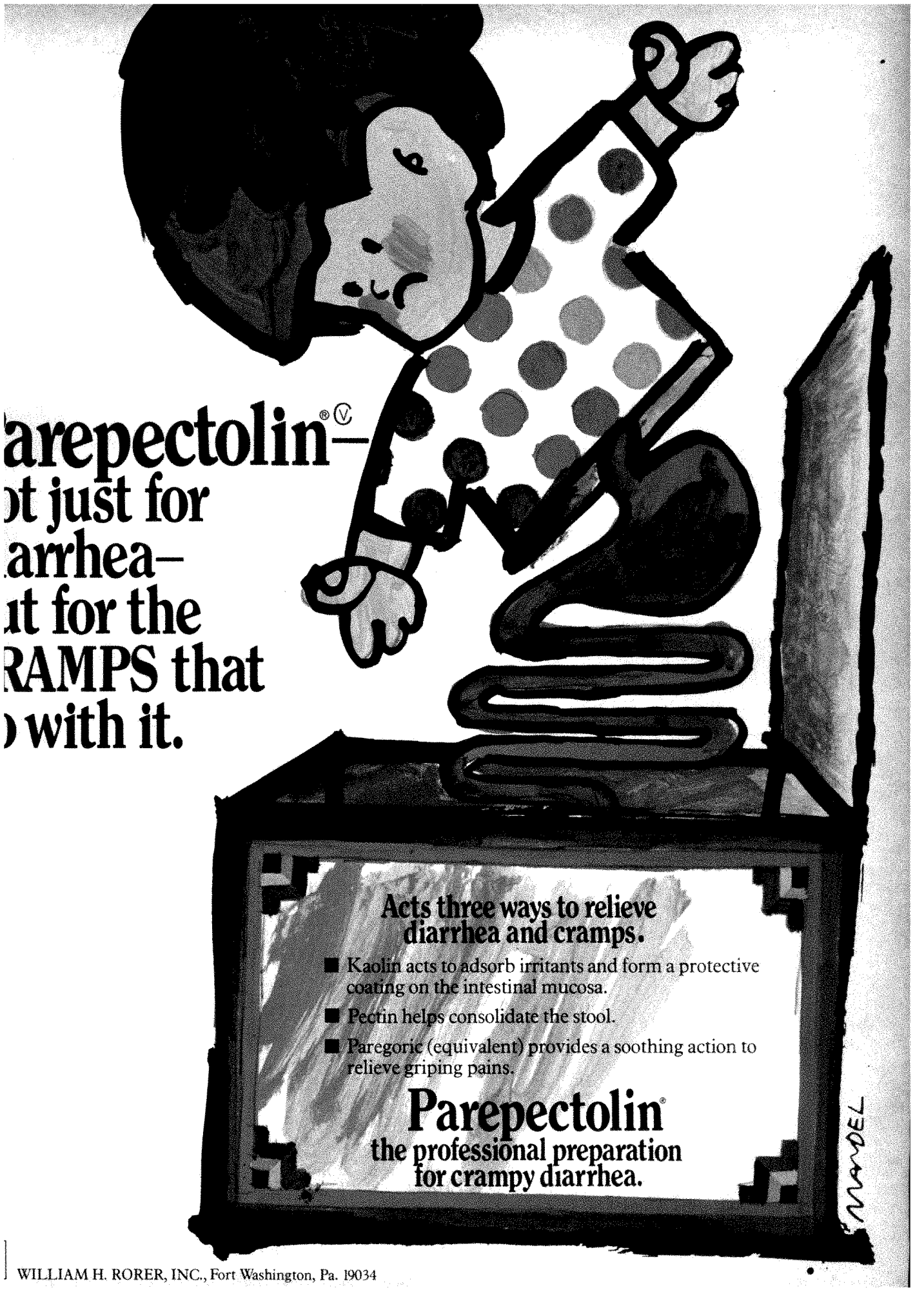
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PRESCRIPTION INDICATIONS: • acute coryza • vasomotor rhinitis • acute eustachian salpingitis • aerotitis (barotitis) media • serous otitis media with eustachian tube congestion

In the following conditions, adjunctive therapy with analgesics, antihistaminics, antibiotics, expectorants and other measures may be employed with Sudafed brand Pseudoephedrine Hydrochloride for optimum results: • allergic rhinitis • asthma • croup • acute otitis media • acute and subacute sinusitis • acute tracheobronchitis

PRECAUTION: Although pseudoephedrine is virtually without pressor effect in normotensive patients, it should be used with caution in hypertensives.

SIDE EFFECTS: While the great majority of patients will experience no side effects, those particularly sensitive to sympathomimetic drugs may note mild stimulation.

decongestion without drowsiness

SUDAFED®
pseudoephedrine HCl
30 mg/5cc Syrup



For allergic dermatoses with strong emotional overlay

Include Atarax® Syrup in the regimen (hydroxyzine HCl)

10 mg per 5 ml, ethyl alcohol 0.5% v/v

- rapid antianxiety action
- demonstrated antihistaminic/antipruritic activity

Contraindications: Hypersensitivity to hydroxyzine. Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit, induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Clinical data in human beings are inadequate to establish safety in early pregnancy. Until such data are available, hydroxyzine is contraindicated in early pregnancy.

Precautions: Hydroxyzine may potentiate the action of central nervous system depressants such as meperidine and barbiturates. In conjunctive use, dosage for these drugs should be reduced. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery.

Adverse Reactions: Drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon dosage reduction. Dryness of the mouth may occur with higher doses. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.



Supply: Tablets, containing 10 mg, 25 mg, or 50 mg hydroxyzine hydrochloride, 100's and 500's; Tablets, containing 100 mg, 100's; Syrup, containing 10 mg per teaspoonful (5 ml) and ethyl alcohol 0.5% v/v, pint bottles.

Before prescribing or administering, see package circular.

ROERIG Pfizer

A division of Pfizer Pharmaceuticals
New York, New York 10017

Brief Summary of Prescribing Information

Actions: Pyrvinium pamoate appears to exert its anthelmintic effect by preventing the parasite from using exogenous carbohydrates. The parasite's endogenous reserves are depleted, and it dies. Povan is not appreciably absorbed from the gastrointestinal tract.

Indication: Povan is indicated for the treatment of enterobiasis.

Warnings: No animal or human reproduction studies have been performed. Therefore, the use of this drug during pregnancy requires that the potential benefits be weighed against its possible hazards to the mother and fetus.

Precautions: To forestall undue concern and help avoid accidental staining, patients and parents should be advised of the staining properties of Povan. Care should be exercised not to spill the suspension because it will stain most materials. Tablets should be swallowed whole to avoid staining of teeth. Parents and patients should be informed that pyrvinium pamoate will color the stool a bright red. This is not harmful to the patient. If emesis occurs, the vomitus will probably be colored red and will stain most materials.

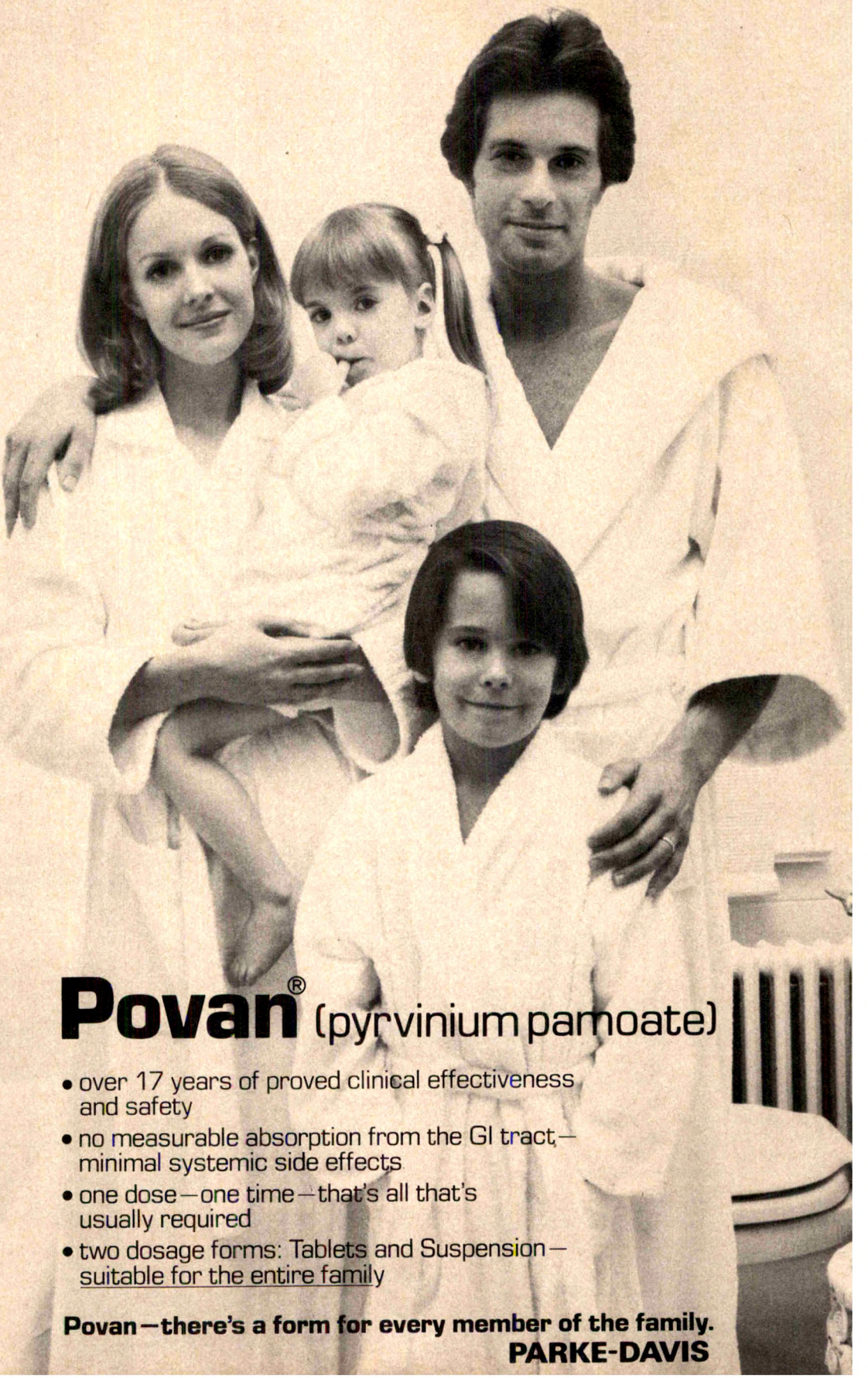
Adverse Reactions: Nausea, vomiting, cramping, diarrhea, and hypersensitivity reactions (photosensitization and other allergic reactions) have been reported. The gastrointestinal reactions occur more often in older children and adults who have received large doses. Emesis is more frequently seen with Povan Suspension than with Povan Filmseals.

How Supplied: Each Povan Filmseal® contains pyrvinium pamoate equivalent to 50 mg pyrvinium, supplied in bottles of 50 (NDC 0710-0747-50; NSN 6505-00-134-1966). Povan Suspension, a pleasant-tasting, strawberry-flavored preparation containing pyrvinium pamoate equivalent to 10 mg pyrvinium per milliliter, is supplied in 2-oz bottles (NDC 0071-1254-31; NSN 6505-00-890-1093).

RC/RD PD-JA-1699-2-P (8-76)

Parke, Davis & Company
Detroit, Michigan 48232

When it's pinworms, treat the family

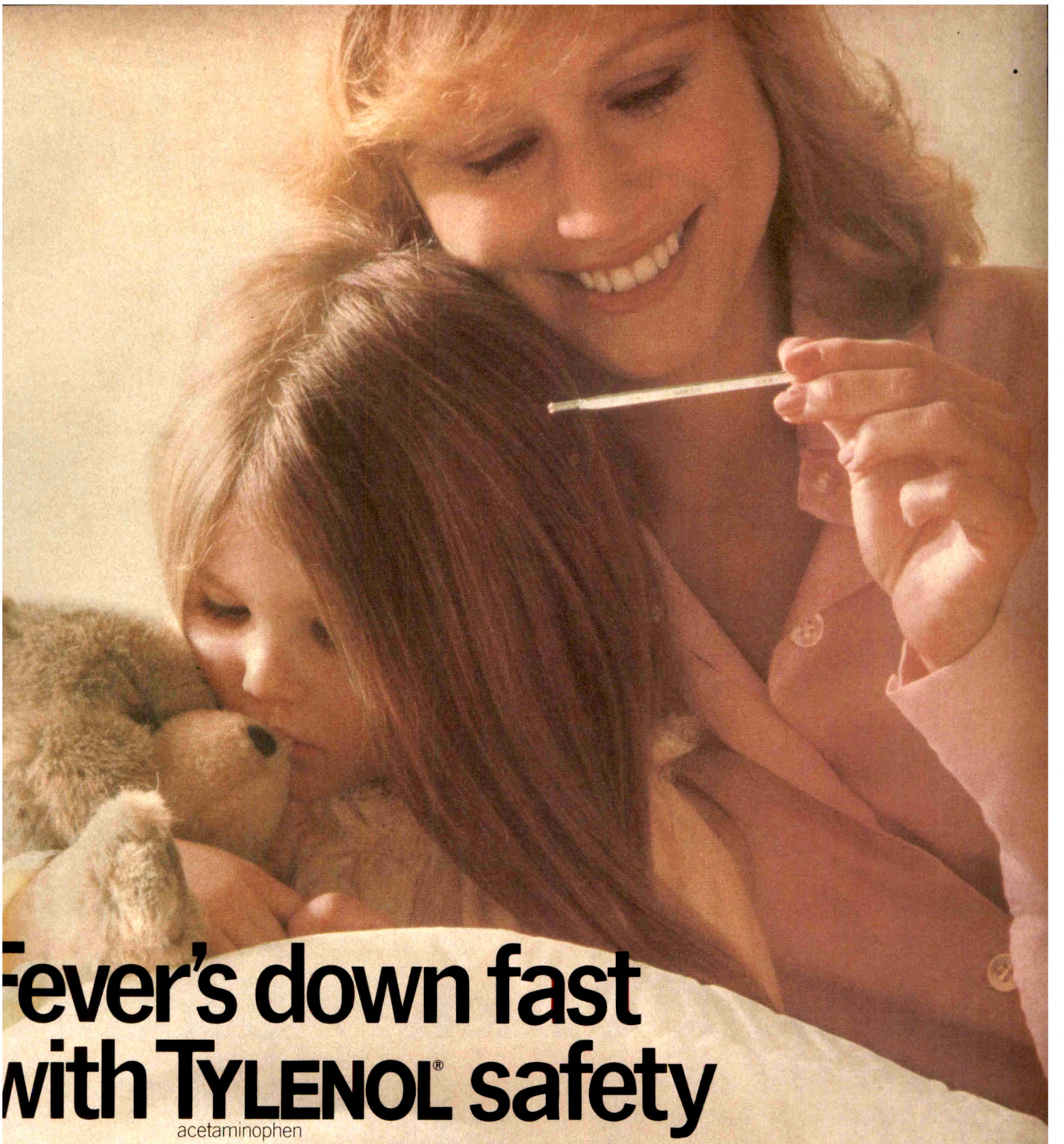


Povan® (pyrvinium pamoate)

- over 17 years of proved clinical effectiveness and safety
- no measurable absorption from the GI tract—minimal systemic side effects
- one dose—one time—that's all that's usually required
- two dosage forms: Tablets and Suspension—suitable for the entire family

Povan—there's a form for every member of the family.

PARKE-DAVIS

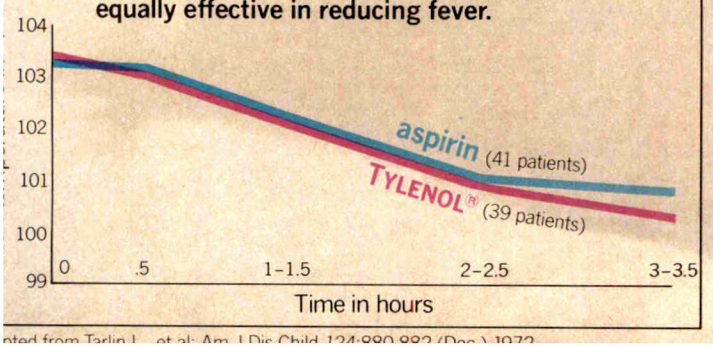


Fever's down fast with TYLENOL® safety

acetaminophen

inical evidence:

TYLENOL® acetaminophen and aspirin are equally effective in reducing fever.





your logical first choice for fever and pain

McNEIL

McNeil Consumer Products Company



A new indication for Septra

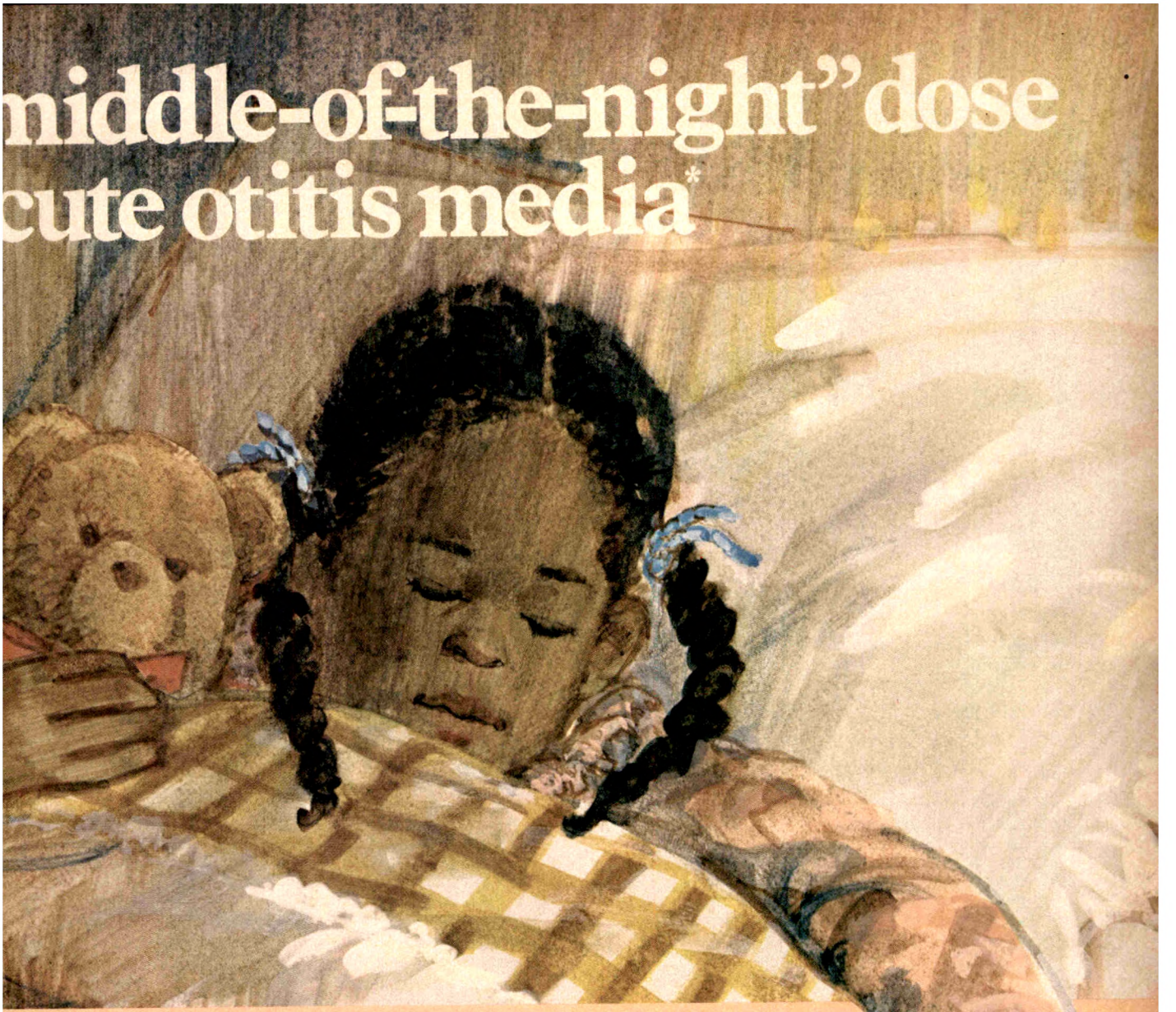
Getting a child with an earache off to sleep is hard enough, without getting her up again. With the q.i.d. and t.i.d. dosages of other antibacterials for acute otitis media, expecting compliance may be expecting a lot. Septra b.i.d. dosage convenience can change all that.

In a study of 94 children with bacterial otitis media confirmed by culture, Septra Suspension produced a success rate of 95.7%.†

Septra Suspension has proved highly effective in acute otitis media caused by the most common middle ear pathogens—*Haemophilus influenzae* and *Streptococcus pneumoniae.*

Though crystalluria has not been a problem with Septra, adequate fluid intake should be maintained and frequent urinalyses with careful microscopic examination performed during therapy. Septra is contraindicated in infants under two months. **Septra should not be used in the treatment of streptococcal pharyngitis.**

†Data on file, Medical Department, Burroughs Wellcome Co.
See last page of this advertisement for prescribing information.



middle-of-the-night" dose cute otitis media*

Septra®

Suspension

Each teaspoonful (5 ml) contains:
40 mg trimethoprim and 200 mg sulfamethoxazole

b.i.d.

through-the-night efficacy against major middle ear pathogens

*Septra is now indicated for use in acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in the judgment of the physician Septra offers some advantage over the use of other antimicrobial agents. Limited clinical information is presently available on the effectiveness of treatment of otitis media with Septra when the infection is due to *Haemophilus influenzae* resistant to ampicillin. To date, there are limited data on the safety of repeated use of Septra in children under two years of age. Septra is not indicated for prophylactic or prolonged administration in otitis media at any age.



Septra® introduces b.i.d. dosage convenience to the treatment of acute otitis media in children

Septra® Suspension

Each teaspoonful (5 ml) contains:
40 mg trimethoprim and 200 mg sulfamethoxazole

- effective *in vitro* against major middle ear pathogens—*Haemophilus influenzae,* including ampicillin-resistant strains, and *Streptococcus pneumoniae**
- well tolerated by infants and children† (Contraindicated in infants under two months. See brief summary below for possible adverse reactions.)

Septra® Tablets

Each tablet contains:
80 mg trimethoprim and 400 mg sulfamethoxazole

- available in pleasant tasting cherry-flavored suspension or in tablet form for use in older children
- encourages compliance; unlike other antibacterials for otitis media, Septra requires no middle-of-the-night dose

---

Septra® Tablets and Suspension

Indications and Usage:

ACUTE OTITIS MEDIA: **For the treatment of acute otitis media in children due to susceptible strains of** *Haemophilus influenzae* **or** *Streptococcus pneumoniae* **when in the judgment of the physician Septra offers some advantage over the use of other antimicrobial agents. Limited clinical information is presently available on the effectiveness of treatment of otitis media with Septra when the infection is due to** *Haemophilus influenzae* **resistant to ampicillin. To date, there are limited data on the safety of repeated use of Septra in children under two years of age. Septra is not indicated for prophylactic or prolonged administration in otitis media at any age.**

Contraindications: Hypersensitivity to trimethoprim or sulfonamides. Pregnancy and during the nursing period. Infants less than two months of age.

Warnings: SEPTRA SHOULD NOT BE USED IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS.

Clinical studies have documented that patients with Group A β-hemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with Septra than do those patients treated with penicillin as evidenced by failure to eradicate this organism from the tonsillopharyngeal area.

Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias. Experience with trimethoprim alone is much more limited, but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides.

Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBCs are recommended; therapy should be discontinued if a significant reduction in the count of any formed blood element is noted.

Precautions: Use with caution in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur (frequently dose-related). During therapy, maintain adequate fluid intake and perform frequent urinalyses with careful microscopic examination and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Septra. *Blood Dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic Reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal Reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *C.N.S. Reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous Reactions:* Drug fever, chills, and toxic nephrosis with oliguria and anuria. Periarteritis nodosa and L.E. phenomenon have occurred. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia; cross-sensitivity may exist with these agents. In rats, long-term administration of sulfonamides has produced thyroid malignancies.

Dosage and Administration: Not recommended for use in infants less than two months of age.

ACUTE OTITIS MEDIA IN CHILDREN: The recommended dose for children with acute otitis media is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, given in two divided doses every 12 hours for 10 days. The following table is a guideline for the attainment of this dosage using Septra Tablets or Suspension.

Children: Two months of age or older:

Weight		Dose—every 12 hours	
lb	kg	Teaspoonfuls	Tablets
20	9	1 (5 ml)	½
40	18	2 (10 ml)	1
60	27	3 (15 ml)	1½
80	36	4 (20 ml)	2 (or 1 DS tablet)

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual Standard Regimen
15-30	Half of the usual dosage regimen
Below 15	Use Not Recommended

Supplied: SEPTRA TABLETS containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 40, 100, 500 and 1000 tablets; unit dose pack of 100. ORAL SUSPENSION, containing the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole in each teaspoonful (5 ml), cherry flavored—bottle of 450 ml.

Also available in double strength, oval-shaped, pink, scored tablets containing 160 mg trimethoprim and 800 mg sulfamethoxazole—bottles of 60 and unit dose packs of 100.

*Clinical results do not necessarily correspond with *in vitro* data.

†Data on file, Medical Department, Burroughs Wellcome Co.

Wellcome
Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

University of Wisconsin
Home Study Course in

IMMUNODEFICIENCY DISEASES

October 16—December 4, 1978
36 Hours AMA Category 1 Credit

Content includes basic concepts about B cells, T cells, neutrophils, macrophages and complement, and clinical applications. Home study materials include syllabus, text, journal reprints, tape/slide units, and self-assessment tests. Three telephone conferences with Instructor, Sheldon Horowitz, M.D., for questions and discussion. Fee: $200

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Won't mask serious vomiting

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PHOSPHORATED CARBOHYDRATE SOLUTION

will stop uncomplicated nausea and vomiting

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PAEDIATRIC HAEMATOLOGY/ONCOLOGY FELLOWSHIP

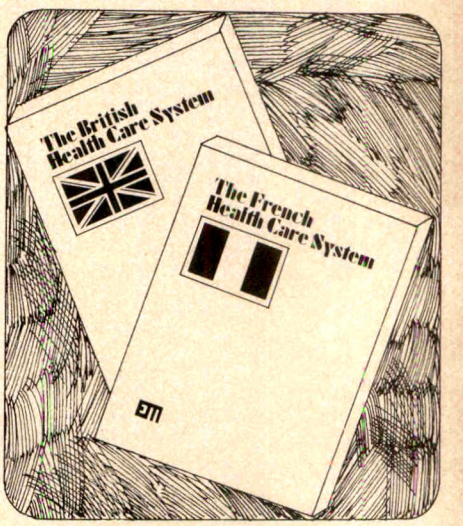
for one year commencing immediately or July 1st, 1979

Paediatric training required. Payment will be equivalent to the resident training level of the applicant. Approved for one year training in paediatrics by the Royal College of Physicians and Surgeons of Canada. Applications will also be accepted for July 1979.

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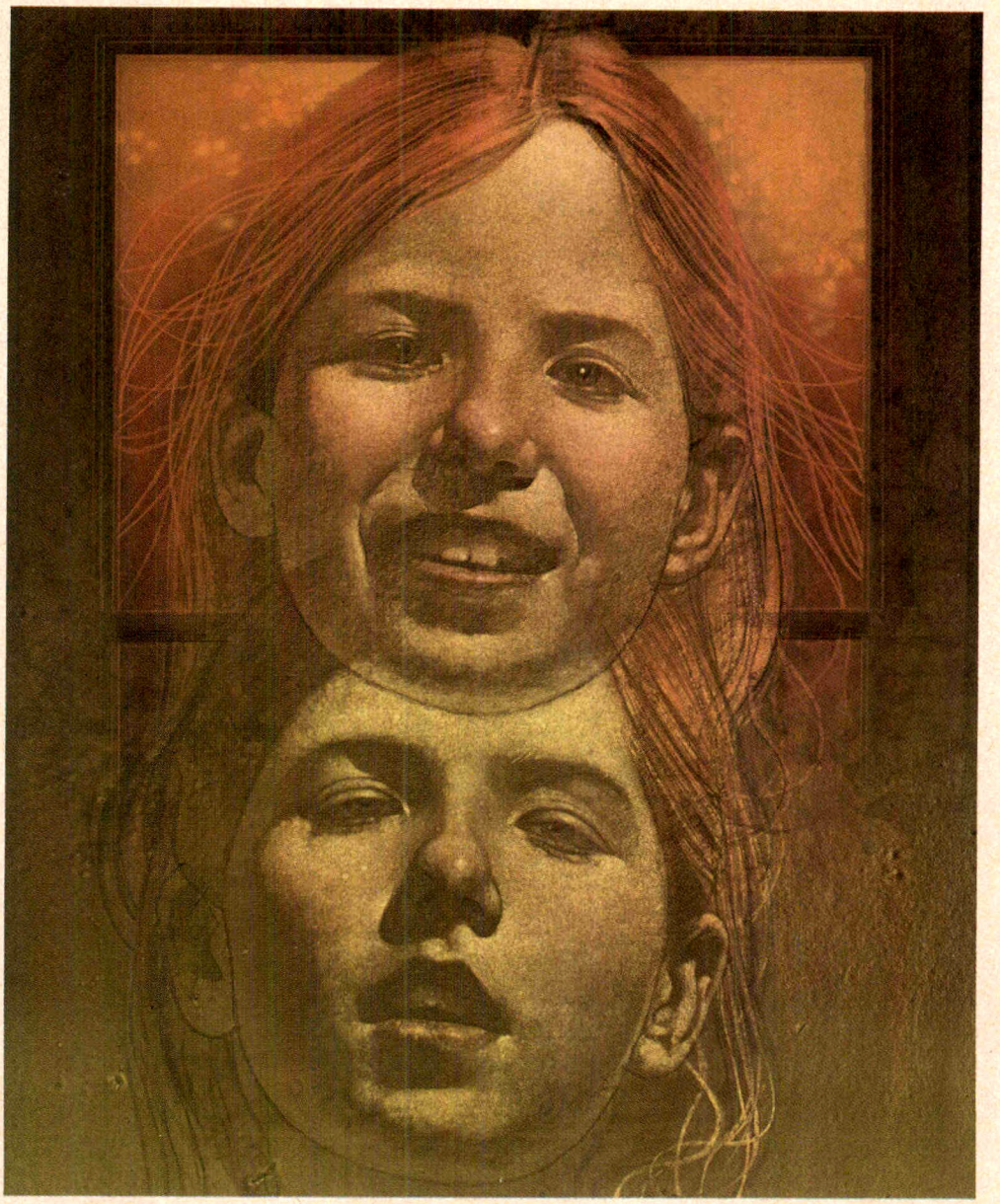
Everyone in the medical profession should read both of these fascinating studies on how other nations have organized the delivery of health care.

Both books will be available Fall of 1976. To order your copies, write ORDER DEPT., AMA, 535 N. DEARBORN ST., CHICAGO, ILL. 60610. **The French Health Care System** (OP-460) costs $3.50; the **British Health Care System** (OP-461), $7.50. The set is $10. Remittance must accompany order.

Depakene®

Valproic Acid

Start with–or add–Depakene. More toxic agents can often be avoided or reduced.



Start with Depakene®

Depakene is indicated for sole or adjunctive therapy in patients with absence seizures, and adjunctively in patients with multiple seizure types that include absence.

With drug-naive patients, the chances are excellent that Depakene will be the only agent needed to control absence seizures.

After a decade of clinical use throughout the world, Depakene has an impressive record of controlling absence seizures, often in patients resistant to other forms of drug therapy. Depakene is considered a drug of choice in many European countries.

Common side effects are relatively mild in context with other agents.

Add Depakene®

Subtract more toxic agents.

Studies show ⅓ to ½ of patients with absence seizures also experience tonic-clonic seizures.[1,2,3] These patients often need multiple drug therapy.

By using Depakene as part of the initial regimen, you can frequently reduce the need for more toxic agents, and extend your range of therapy from the start of treatment.

Complete prescribing information can be found on the following page along with full disclosure.

1. Sato, S., Dreifuss, F.E., Penry, J.K., Prognostic factors in absence seizures., Neurology, 26:788-796, 1976.
2. Livingston, S., Torres, I., Pauli, L.L., et al, Petit mal epilepsy. Results of a prolonged follow-up study of 117 patients., JAMA, 1974:113-118, 1965.
3. Currier, R.D., Kooi, K.A., Saidman, L.J., Prognosis of "pure" petit mal. A follow-up study., Neurology (Minneap) 13:959-967, 1963.

ABBOTT

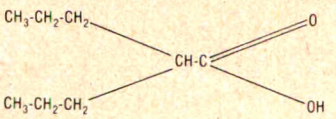
8073265

Depakene®
Valproic Acid

ABBOTT

DESCRIPTION

DEPAKENE (valproic acid) is a carboxylic acid designated as 2-propylpentanoic acid. It is also known as dipropylacetic acid. DEPAKENE has the following structure:



Valproic acid (pKa 4.95) has a molecular weight of 144 and occurs as a colorless liquid with a characteristic odor. It is slightly soluble in water (1.3 mg/ml) and very soluble in organic solvents.

DEPAKENE is supplied as soft elastic capsules and syrup for oral administration.

CLINICAL PHARMACOLOGY

DEPAKENE is an anticonvulsant agent which is chemically unrelated to other drugs used to treat seizure disorders. It has no nitrogen or aromatic moiety characteristic of other anticonvulsant drugs. The mechanism by which DEPAKENE exerts its anticonvulsant effects has not been established. It has been suggested that its activity is related to increased brain levels of gamma-aminobutyric acid (GABA). The effect on the neuronal membrane is unknown.

DEPAKENE is rapidly absorbed after oral administration. Peak serum levels of valproic acid occur approximately one to four hours after a single oral dose of DEPAKENE. The serum half-life ($t_{0.5,s}$) of the parent compound is approximately eight to twelve hours. A slight delay in initial absorption occurs when the drug is administered with meals but this does not affect the total absorption.

A good correlation has not been established between daily dose, serum level and therapeutic effect. Valproic acid is rapidly distributed and the drug is strongly bound (90%) to human plasma proteins.

Elimination of DEPAKENE and its metabolites occurs principally in the urine, with minor amounts in the feces and expired air. Very little unmetabolized parent drug is excreted in the urine. The drug is primarily metabolized in the liver and is excreted as the glucuronide conjugate. Other metabolites in the urine are products of beta and omega oxidation (C-3 and C-5 position). The three major oxidative metabolites are 2-propyl-3-keto-pentanoic acid, 2-propyl-5-hydroxypentanoic acid, and 2-propyl-glutaric acid.

INDICATIONS

DEPAKENE (valproic acid) is indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, including petit mal. DEPAKENE may also be used adjunctively in patients with multiple seizure types which include absence seizures.

In accordance with the International Classification of Seizures, simple absence is defined as very brief clouding of the sensorium or loss of consciousness (lasting usually 2-15 seconds), accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

CONTRAINDICATIONS

DEPAKENE (valproic acid) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

Liver dysfunction including hepatic failure resulting in fatalities has occurred in a few patients receiving DEPAKENE and concomitant anticonvulsant drugs. These incidences have occurred during the first six months of treatment with DEPAKENE. Although a causal relationship has not been established, liver function tests should be performed prior to therapy and every two months thereafter. Caution should be observed when administering DEPAKENE to patients with pre-existing hepatic disease.

Usage in Pregnancy: THE EFFECTS OF DEPAKENE IN HUMAN PREGNANCY ARE UNKNOWN. ANIMAL STUDIES HAVE DEMONSTRATED TERATOGENICITY.

Studies in rats demonstrated placental transfer of the drug. Doses greater than 65 mg/kg/day given to rats, mice and rabbits produced an increased incidence of skeletal abnormalities of the ribs, vertebrae and palate. In rats, there was a dose-related delay in onset of parturition. Postnatal growth and survival of the progeny was unaffected. Embryolethality or major developmental abnormalities occurred in rats and rabbits at doses of 350 mg/kg/day. Studies are being conducted to determine whether there are differences in the toxicity of DEPAKENE (valproic acid) in pregnant rabbits when compared to non-pregnant rabbits.

Recent reports suggest an association between the use of anticonvulsant drugs by women with epilepsy and an elevated incidence of birth defects in children born to these women. Data are more extensive with respect to phenytoin and phenobarbital, but these are also the most commonly prescribed anticonvulsants; less systematic or anecdotal reports suggest a possible similar association with the use of all known anticonvulsant drugs.

The reports suggesting an elevated incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodologic problems in obtaining adequate data on drug teratogenicity in humans; the possibility also exists that other factors, e.g., genetic factors or the epileptic condition itself, may be more important than drug therapy in leading to birth defects.

The great majority of mothers on anticonvulsant medication deliver normal infants. It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of child-bearing potential.

PRECAUTIONS

General: Because of rare reports of platelet aggregation dysfunction, thrombocytopenia and elevated liver enzymes, liver function tests, platelet counts and bleeding time determination are recommended before initiating therapy and at periodic intervals.

Since DEPAKENE (valproic acid) may interact with concurrently administered anticonvulsant drugs, periodic serum level determinations of concomitant anticonvulsant drugs are recommended during the early course of therapy. (See Drug Interactions).

DEPAKENE is partially eliminated in the urine as a ketone containing metabolite which may lead to a false interpretation of the urine ketone test.

Information For Patients: Since DEPAKENE may produce CNS depression, especially when combined with another CNS depressant (e.g., alcohol), patients should be advised not to engage in hazardous occupations, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Drug Interactions: DEPAKENE may potentiate the CNS depressant activity of alcohol.

THERE IS EVIDENCE THAT DEPAKENE MAY CAUSE AN INCREASE IN SERUM PHENOBARBITAL LEVELS, ALTHOUGH THE MECHANISM OF THE INTERACTION IS UNKNOWN. ALL PATIENTS RECEIVING CONCOMITANT BARBITURATE THERAPY SHOULD BE CLOSELY MONITORED FOR NEUROLOGICAL TOXICITY, SERUM BARBITURATE DRUG LEVELS OBTAINED, IF POSSIBLE, AND THE BARBITURATE DOSAGE DECREASED, IF APPROPRIATE.

THERE IS CONFLICTING EVIDENCE REGARDING THE INTERACTION OF DEPAKENE WITH PHENYTOIN. IT IS NOT KNOWN IF THERE IS A CHANGE IN UNBOUND (FREE) PHENYTOIN SERUM CONCENTRATIONS. THE DOSAGE OF PHENYTOIN SHOULD BE ADJUSTED AS REQUIRED BY THE CLINICAL SITUATION.

THE CONCOMITANT USE OF VALPROIC ACID AND CLONAZEPAM MAY PRODUCE ABSENCE STATUS.

Caution is recommended when DEPAKENE (valproic acid) is administered with drugs affecting coagulation, e.g., aspirin and warfarin. (See ADVERSE REACTIONS).

Carcinogenesis, Mutagenesis: There has been insufficient study of the drug in animals to determine whether it has carcinogenic potential. Carcinogenicity studies in rats and mice are currently in progress.

Mutagenesis studies on DEPAKENE have been performed using bacterial and mammalian systems. These studies have provided no evidence of a mutagenic potential for DEPAKENE.

Pregnancy: See WARNINGS.

Nursing Mothers: DEPAKENE is excreted in breast milk. It is not known what effect this would have on a nursing infant. As a general rule, nursing should not be undertaken while a patient is receiving DEPAKENE.

Fertility: Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses greater than 350 mg/kg/day in rats and greater than 90 mg/kg/day in dogs. THE EFFECT OF DEPAKENE (VALPROIC ACID) ON THE DEVELOPMENT OF THE TESTES AND ON SPERM PRODUCTION AND FERTILITY IN HUMANS IS UNKNOWN.

ADVERSE REACTIONS

Since DEPAKENE (valproic acid) has usually been used with other anticonvulsant drugs, it is not possible, in most cases, to determine whether the following adverse reactions can be ascribed to DEPAKENE alone, or the combination of drugs.

Gastrointestinal: The most commonly reported side effects at the initiation of therapy are nausea, vomiting and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps and constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported.

CNS Effects: Sedative effects have been noted in patients receiving valproic acid alone but are found most often in patients receiving combination therapy. Sedation usually disappears upon reduction of other anticonvulsant medication. Ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes", tremor, dysarthria, dizziness, and incoordination have rarely been noted. Rare cases of coma have been noted in patients also on phenobarbital.

Dermatologic: Transient increases in hair loss have been observed. Skin rash and petechiae have rarely been noted.

Psychiatric: Emotional upset, depression, psychosis, aggression, hyperactivity and behavioral deterioration have been reported.

Musculoskeletal: Weakness has been reported.

Hematopoietic: Valproic acid inhibits the secondary phase of platelet aggregation. (See Drug Interactions). This may be reflected in altered bleeding time. Relative lymphocytosis and mild thrombocytopenia have also been noted in isolated cases. Leukopenia has been reported.

Hepatic: Increases in serum alkaline phosphatase and elevations of serum glutamic oxaloacetic transaminase (SGOT) have been noted. Isolated cases of severe hepatotoxicity have been reported. (See WARNINGS).

OVERDOSAGE

A single case of overdosage with valproic acid has been reported. After ingesting 36 grams in combination with phenobarbital and phenytoin, the patient presented in deep coma. An electroencephalogram recorded diffuse slowing, compatible with the state of consciousness. The patient made an uneventful recovery.

Since DEPAKENE is absorbed very rapidly, gastric lavage may be of limited value. General supportive measures should be applied with particular attention being given to the maintenance of adequate urinary output.

DOSAGE AND ADMINISTRATION

DEPAKENE (valproic acid) is administered orally. The recommended initial dose is 15 mg/kg/day increasing at one week intervals by 5 to 10 mg/kg/day, until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 30 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in a divided regimen.

The following table is a guide for the initial daily dose of DEPAKENE (valproic acid) (15 mg/kg/day):

Weight (kg)	Weight (lb)	Total Daily Dose (mg)	Number of Capsules or Teaspoonfuls of Syrup Dose 1	Dose 2	Dose 3
10 — 24.9	22 — 54.9	250	0	0	1
25 — 39.9	55 — 87.9	500	1	0	1
40 — 59.9	88 — 131.9	750	1	1	1
60 — 74.9	132 — 164.9	1,000	1	1	2
75 — 89.9	165 — 197.9	1,250	2	1	2

As the DEPAKENE dosage is titrated upward, blood levels of phenobarbital and/or phenytoin may be affected. (See PRECAUTIONS).

Patients who experience G.I. irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level.

THE CAPSULES SHOULD BE SWALLOWED WITHOUT CHEWING TO AVOID LOCAL IRRITATION OF THE MOUTH AND THROAT.

HOW SUPPLIED

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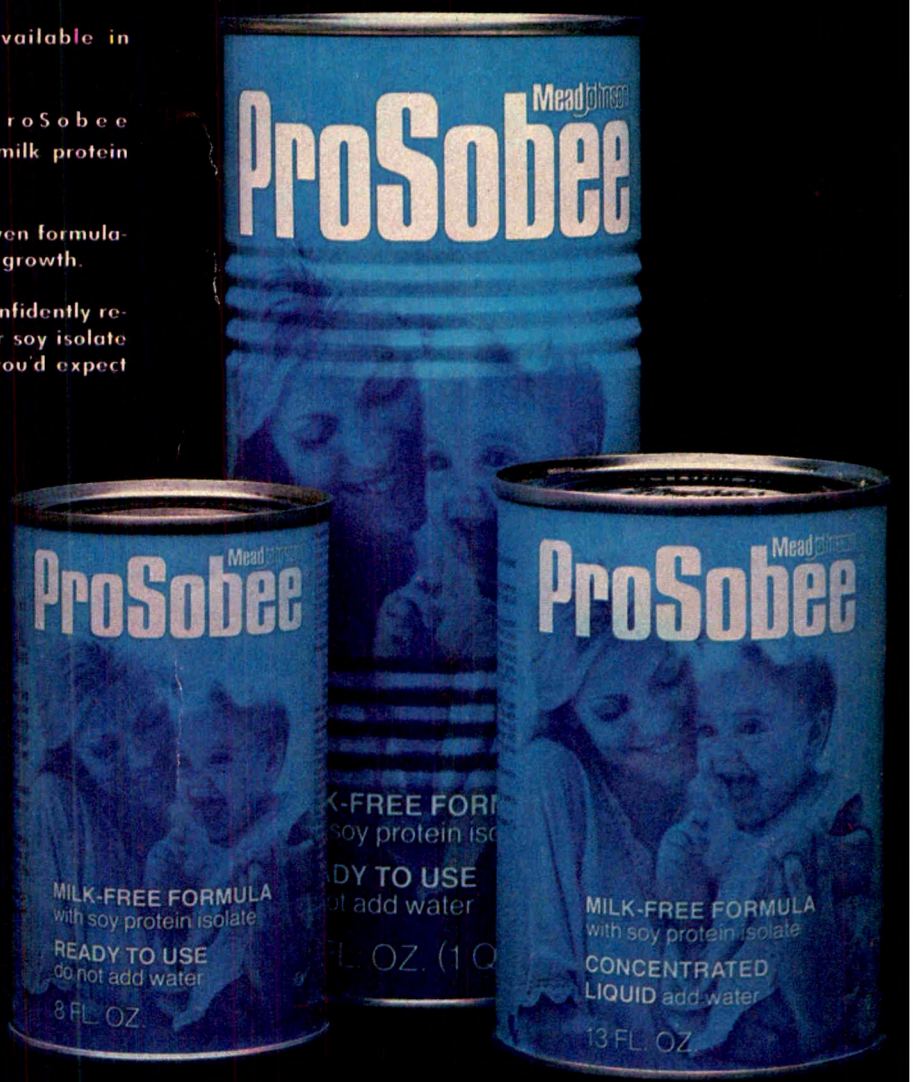
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Bicarbonate Therapy Revisited

A Study in Therapeutic Revisionism

Infusion of alkali for the treatment of neonatal acidosis has been a standard practice in delivery rooms and neonatal intensive care units for the past 15 years. The ready availability of vials of hyperosmolal (1 M) sodium bicarbonate has led to the use of this base in the treatment of neonatal asphyxia and the respiratory distress syndrome (RDS). Recent reports of controlled studies, however, prompt reevaluation of this therapeutic approach. In fact, both laboratory and clinical investigations indicate that the routine use of bicarbonate in these clinical situations is rarely efficacious, is frequently dangerous, and may well be contraindicated.

Sodium bicarbonate can function as a buffer because its acid form, H_2CO_3, dissociates into water and a volatile gas, CO_2. Most buffers have a maximum effect on pH when the ratio of dissociated anion to acid is 1:1. The bicarbonate system, however, works well despite a HCO_3/H_2CO_3 ratio of 20:1 due to the rapid elimination of CO_2 by the lungs. The excretion of CO_2 pulls the reaction $H^+ + HCO_3^- \rightleftarrows H_2CO_3 \rightleftarrows H_2O + CO_2$ to the right and thereby permits bicarbonate to play an important role in the buffering of the hydrogen ion. When bicarbonate is added to a system from which CO_2 cannot be eliminated, the pH remains unaffected or decreases "paradoxically" as P_{CO_2} rises.[1,2]

To illustrate the problem created by the addition of bicarbonate to a closed system: an isotonic infusion of 3 mEq of $NaHCO_3$ per kilogram of body weight to an infant with a blood pH of 7.1 will generate approximately 0.43 mmoles of CO_2 per kilogram. As the endogenous production of CO_2 is approximately 0.3 mmole/kg/min, such an infusion of isotonic $NaHCO_3$ will generate an amount of CO_2 equal to that produced endogenously in about 1½ minutes. In a closed system this will raise the P_{CO_2} 15 torr. Moreover, the common clinical practice of infusing bicarbonate as a hypertonic solution will generate additional CO_2 by causing a shift of intracellular water with an increase in intracellular ionic strength and dissociation of hemoglobin.[1]

Clinical situations mimicking a closed system have been documented. Evans et al[3] studied spontaneously breathing acidotic infants who had required resuscitation at birth because of perinatal asphyxia. Infusions of bicarbonate failed to correct the low pH and led to elevations in P_{CO_2}. Corbet et al[4] also studied pH changes in infants who were acidotic following resuscitation and found no difference in the rate of correction of the pH when infusions of bicarbonate were used as compared with dextrose water.

A similar inability of bicarbonate to correct the pH or change the clinical course was noted in infants suffering from RDS.[5,6] Recently Bland et al,[7] in a well-controlled clinical study, confirmed the lack of any therapeutic advantage of bicarbonate infusions in the treatment of RDS; bicarbonate with or without added albumin conferred no benefit greater than dextrose solution alone. Corbet et al[4] reported that acidotic infants suffering from RDS who received bicarbonate had changes in pH similar to those found in infants infused with bicarbonate-free solutions. Moreover, the use of bicarbonate did not decrease mortality.

Previous reports of the efficacy of bicarbonate were either from uncontrolled studies or from an era when currently available neonatal intensive care techniques were not in use.[8,9] Acidosis in RDS can be minimized by such measures as careful maintenance of thermal neutrality, infusion of plasma expanders to maintain blood pressure, ventilatory support with continuous distending pressure to maintain oxygenation, and controlled, assisted ventilation to correct for retention of CO_2. Only when acidosis is persistent and severe (below a pH of 7.15) despite maximum cardiorespiratory support is slow infusion of isotonic buffer warranted.

The lack of any firm evidence for the value of bicarbonate infusion in the treatment of RDS is especially of concern in the light of reports of increased intracranial hemorrhage associated with such infusions.[10,11] Thomas[12] has clearly shown that such hemorrhages correlate with changes in serum osmolality and not with bicarbonate per se. Only when serum osmolality exceeded 320 mOsm/kg of body water did the incidence of hemorrhage increase significantly. Elevation of serum osmolality to such dangerous levels can be reached in clinical practice by infusions of hypertonic bicarbonate solutions. Siegel et

al[13] and Rhodes et al[14] have shown that a single dose of molar bicarbonate (1,800 mOsm/liter) infused at a dose of 3 mEq/kg and at a rate of 1 to 2 ml/min raises serum osmolality 10 mOsm/kg of body water. Baum and Robertson[15] reported that a single dose of 4 mEq/kg of bicarbonate infused over 30 seconds raises the serum osmolality an average of 25 mOsm, clearly into the danger zone.

Finberg[16] has emphasized that three thermodynamic variables—quantity, concentration, and rate—are involved in the relationship of sodium bicarbonate administration to intracranial hemorrhage. Controlling any one of the variables may reduce, if not actually eliminate, the incidence of hemorrhage. Slow infusions of isotonic or hypotonic bicarbonate solutions have not been associated with increases in intracranial hemorrhage[4] or serum osmolality.[15] However, repeated administration of $NaHCO_3$ and other sodium-containing solutions may in time lead to hypernatremia, hyperosmolarity, and the associated CNS complications.[10]

The risk of rapid infusion of hypertonic solution raises questions regarding the well-established practice of infusing intravenous bicarbonate during the course of resuscitation. The evidence to support the use of buffer rests on the monkey experiments of Dawes and co-workers[17,18] who demonstrated that infusion of hypertonic base sustained cardiorespiratory function during asphyxia and shortened recovery time following resuscitation. In addition, monkeys who received base had substantially less brain damage than those treated with ventilation alone. However, intracranial hemorrhage was a common finding in the monkeys infused with bicarbonate, and similar CNS hemorrhages have been reported after successful resuscitation of asphyxiated human newborns.[19]

The data just cited prompt the suggestion that only isotonic solutions of base be used during a resuscitation. To date, no controlled studies comparable to Dawes's experiments but using isotonic solution have been published. However, the quantity of base required for buffering is dictated by the degree of acidosis and is unaffected by the concentration of base. As the exigencies of an emergency resuscitation require a rapid infusion, dilution of the bicarbonate solution seems both practical and safe. Moreover, the increase in fluid load (10 to 15 ml/kg in typical dose) would help correct the hypotension that is part of the asphyxia syndrome.[17,20] Either molar bicarbonate diluted with five parts water (300 mOsm/liter) or a mixture of tromethamine, sodium chloride, and potassium chloride (THAM-E) 0.3 M (367 mOsm/liter) can be used as the buffer solution during resuscitation. It must be stressed, however, that use of either preparation should be reserved for those infants who do not respond to ventilation alone, as evidenced by a persistent bradycardia (pulse rate below 80 beats per minute) and hypotension. In the absence of circulatory collapse, rapid infusion of any base is not warranted.

In summary, infusion of bicarbonate in the treatment of neonatal acidosis has limited value. Although it may be a useful adjunct in the resuscitation of severely depressed and acidotic infants, its efficacy in the management of postasphyxia acidosis or RDS is not supported by any data. The clear risks and disadvantages of such infusions should warn against its current indiscriminate use.

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Sodium bicarbonate—*Ion-O-Trate Sodium Bicarbonate, Neut.*

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Recent Advances in Viral Diagnosis

On Jan 12 and 13, 1978, a workshop on new and useful methods in viral diagnosis was held at the National Institutes of Health, Bethesda, Md, sponsored by the National Institute of Allergy and Infectious Disease and the North American Group for Rapid Viral Diagnosis. The workshop was designed to review recent advances in viral diagnostic techniques, a subject which should be of interest to all practicing pediatricians. The last decade has seen the development of a number of methods that have accelerated the time between the submission of a specimen by a clinician and the reception of useful information on the presence and nature of an infecting virus. Because of these advances, it is quite possible that in the next decade viral diagnosis will become inexpensive, rapid enough to be clinically useful, and widely available to clinicians in the United States. It is the purpose of this MARGINAL COMMENT to review briefly the areas in which advances have been made and to point out where there is clear promise of advances in the future.

Traditional viral diagnosis has depended on analysis of acute and convalescent serums or on the culture and subsequent recognition of viruses from clinical specimens. Serologic diagnosis almost always gives a diagnosis only in retrospect. Cultural techniques require the growth and maintenance of tissue cultures, a technology considered outside the capacity of most microbiology laboratories. Moreover, the time required to recognize virus growth, has been considered impractically long, although in our experience this assumption has frequently proved to be wrong. Most of the new techniques attempt to circumvent this virus growth procedure by the detection of antigens (as opposed to live infectious viruses) in body fluids.

One new method that has been clearly proved useful is that of immunofluorescence. Professor Phillip S. Gardner of the Royal Victoria Infirmary, Newcastle-upon-Tyne, England, has pioneered this field and demonstrated that immunofluorescence could be used to identify viruses in respiratory secretions rapidly, precisely, and with great sensitivity. The technique depends on the demonstration of viral antigens in cells shed from the respiratory mucosa. Epithelial cells, collected by aspiration of nasal mucus, are stained for specific viral antigen using animal serums and fluorescein-conjugated antiglobulins. Professor Gardner detects respiratory viruses as often as or more often than they can be cultured in tissue culture, usually giving the clinician the specific diagnosis on the same day as the specimen was obtained.

The technique can be used on slides made in an outlying hospital and then sent by mail to his laboratory. He has demonstrated the feasibility of this technique in the identification of influenza virus, parainfluenza viruses, respiratory syncytial virus, adenovirus, measles, mumps, and even coronaviruses in respiratory secretions. Others have developed the technique for rubella, cytomegalovirus, varicella zoster virus, and herpes simplex.

Despite this impressive record, fluorescence has never been widely practiced for viral diagnosis within this country. The technique requires specific antiserums of high quality, many of which are not available commercially at the present time. Moreover, an expensive instrument, a fluorescence microscope, must be used, and careful training of the fluorescence microscopist is an absolute necessity. These requirements tend to limit its application to a few academic and tertiary medical centers. There is, however, no good reason why application should not become more widespread, particularly if high quality serums become commercially available and if the benefits of such diagnosis are shown to be economically important in the care of hospitalized children. As discussed below, however, other techniques for identification of viruses in clinical specimens may become available that are simpler and less expensive, and fluorescence may be reserved for special situations.

Other methods for detection of viral antigens in clinical specimens have been pioneered in those diseases where virus culture has been unsuccessful. These are, in particular, hepatitis A and B and viral diarrheas. In these diseases, virologists have been forced to develop strategies that do not depend on the capacity of cell culture or laboratory animals to support viral replication. The techniques of greatest use are ones that detect very small amounts of free viral antigen in body fluids.

These techniques fall into two broad categories. First, there are those that maximize the speed and sensitivity of a single antigen-antibody reaction. Examples of this are counter immunoelectrophoresis (CIE, widely used in detection of bacterial antigens), and tests where antibody is attached to the surface of larger particles, such as latex balls or erythrocytes (indirect hemagglutination tests) so that the immunologic reaction is magnified to become visible to the naked eye. The second category involves the use of two or more different antibodies, often added in a "sandwich" so that they attach to the antigen in several places or even to each other, augmenting the sensitivity of the reaction at each step.

Both CIE and indirect hemagglutination have been used with success in detection of hepatitis B virus, and CIE has been recently applied to fecal rotaviruses. They are practical methods because they are simple and rapid (complete in a few hours) and require few articles of expensive equipment. They are, however, less sensitive than the second, sandwich, group of techniques.

The two most widely applied sandwich techniques are radioimmunoassays (RIA) and enzyme-linked immunosorbent assays (ELISA). In both systems, one species of antiviral anti-

body (the "capture" antibody) is attached to a solid surface, such as a plastic well or tube, and the clinical specimen is then added. The virus is allowed to attach, and then an antibody or series of antibodies is added on top. The final antibody layer is labelled in some way, either with iodine 125 (for RIA), or by conjugation with an enzyme that produces a color reaction when the appropriate substrate is added (for ELISA). Radioactivity, in the former system, or color in the latter signals the presence of antigen (virus) in the specimen.

Radioimmunoassay techniques are now widely available for detection of hepatitis B antigen. Enzyme-linked immunosorbent assays however, offer the distinct advantage that a γ-radioactivity counter is not necessary; the color change can be qualitatively detected by eye and quantitatively measured with a spectrophotometer, available in most hospital chemistry laboratories. This test can also be completed quickly, usually in four to 24 hours.

Enzyme-linked immunosorbent assay techniques of great sensitivity have been developed for detection of hepatitis A and B viruses and rotaviruses in stool. A method has been recently described for detecting herpes simplex virus in skin vesicles. The technique holds promise for rapid and inexpensive virologic diagnosis of many other viral diseases, including respiratory illness, other gastrointestinal infections, and perhaps other herpetic conditions. As long as the antiserums and plastics used are of a high quality, the tests are almost "goof-proof."

Considerable work still must be done to develop the full potentiality of these tests, and after this to make them practical and cheap. For some viruses this may never happen, and we may be forced to rely on the traditional methods of tissue culture identification. An optimist's view is, however, that, before too long, clinicians will have available in their hospital laboratories the capability to identify quickly and precisely many of the viral illnesses of childhood. If this does indeed occur, then we can hope for more rational use of antibiotics, better control of hospital-acquired infections, and the eventual disappearance of that waste-basket diagnosis, the "viral syndrome."

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Use of Modified Food Starches in Infant Nutrition

Modified food starches (MFS) are food additives used to impart functional properties to food products. Modified food starches are used primarily in strained and junior foods and to a minor extent in infant formulas, such as soybean (Isomil). Recently, the American Academy of Pediatrics subcommittee, under contract to the Food and Drug Administration, held a conference on the use and safety of MFSs in infant nutrition. (The subcommittee on evaluation of safety of modified starches in infant foods, committee on nutrition, American Academy of Pediatrics.[1]) This comment is based in part on the subcommittee's recommendations.

Interest in the MFS arises from three principal concerns. The first relates to the bioavailability of the starch itself. The second is the potential that undigestible starch may have for producing diarrheal symptoms, malabsorption, and changes in gastrointestinal (GI) flora. The third is the toxicological effect of the chemicals used to modify the starch and their possible mutagenic and carcinogenic properties.

There have been few long-term studies to delineate the effect of starch feeding on the growth of young infants. Nonetheless, during the past half a century, there has been an increasing tendency to introduce solid foods (beikost) to infants very early in life, and many infants receive cereal and other carbohydrate-containing foods as early as the first, second, and third weeks of life. As a result, abnormally loose stools are not uncommon in these infants. Is this deleterious to the infant? The answer to this important question is not known.

The digestion and absorption of starches is best discussed by considering the physical and chemical nature of native and modified starches. Starch is a polymer of anhydroglucose units linked together to form either the linear polymer, amylose, or the branched polymer, amylopectin. An abundance of hydroxyl groups impart an affinity for water to the starch, and this results in associations between molecules through hydrogen bonding. This bonding results in the formation of an intermolecular network in which water is entrapped producing a gel. Starches, such as corn, tapioca, and potato, contain about 18% to 27% amylose and the remainder is amylopectin. When starch granules in water are heated with agitation, the granules undergo irreversible swelling. Modified starches were developed primarily to overcome the high viscosity opacity and tendency to form gel resulting in an undesirable texture that limits consumer acceptability. The basic premise behind the modifications is to alter the starches so they can meet the critical needs of the food industry in terms of quality, processing, packaging, and distribution while retaining the nutritive value of the native starch.

Modified food starches in baby food can be described simply as an effective stabilizer. A stabilizer is an essential component of baby foods, required to suspend the finely divided food particles and provide a desirable product from the standpoints of feeding consistency, texture, appearance, distribution of nutrients, and storage stability. Flexibility in caloric density is also provided as well as flavor intensity in highly flavored foods. If MFSs did not have considerable advantages to the food industry, MFSs would never have assumed the role that they have in the production of baby foods. Modified food starch concentrations in baby foods are from 5% to 6½%, and their addition is considered to be "good manufacturing particles."[1]

There are four basic types of modifying treatments: bleaching, conversions, crosslinking, and stabilizing.[1,2] By subjecting waxy maize and tapioca to one or more of these modifying treatments, various MFSs result. The starch modifications used at the present time in the United States include waxy maize (distarch phosphate, acetylated distarch adipate, and acetylated distarch phosphate) and tapioca (distarch phosphate and acetylated distarch phosphate). As used, MFS supplies 10% to 32% of the total energy available from these foods. Pertinent information concerning MFS use includes data on total consumption and estimates of use ranges of specific MFSs. It is possible to calculate that jars of individual foods could contain as high as 9.4 g of MFS per strained food jar, and 15.4 g per junior-size food jar. Intakes as high as 29 g a day of MFS could be derived from this source.[3] It is claimed by the food industry, that the level of crosslinking used in MFS does not change the in vivo digestibility of the starch in animal studies.[1] However, in these studies, it was shown that noticeable reductions in in vitro digestibility occurred when higher degrees of crosslinking was used.

At the present, no clinical data assessing MFS digestibility in human infants are available. In considering the digestibility of MFS, it is useful to review the limited available data on the digestion of starch in infants. There are many factors involved in starch digestion and absorption. These include salivary α-amylase activity, gastric emptying rate, pancreatic α-amylase activity and its distribution in the GI tract, physicochemical properties of the succus entericus and the unstirred layer, intestinal motility, intestinal mature epithelial cell brush border glucoamylase and maltase activities, and glucose absorption and use.[4] The relative importance of these factors are difficult to evaluate because of scant information on their development during infancy. Pancreatic α-amylase has a potential rate-limiting effect, since it hydrolyzes amylose and amylopectin, at random, to maltose, maltotriose, and maltotetrose. Thus, the lack of pancreatic amylase activity in the duodenal fluids in the first three months of life and the very low pancreatic activity up to 6 months of age, is a cause for concern.[4]

Many infants receive cereal and fruit during the first two or three weeks of life, and abnormally loose stools are not uncommon in these young infants. Severe iatrogenic diarrhea and growth failure due to physiologic absence of pancreatic α-amylase have been described.[5] In this report, dietary starch seemed to be an important factor in impairing the infant's weight gain. The failure to thrive was not due to an exogenous caloric deficiency of food, even excluding the calories derived from starch. This suggests that the undigested starch interfered with absorption of other food ingredients and represents an exaggeration of the physiologic pancreatic amylase deficiency, which occurs to some degree in all infants. In infants as old as 6 months of age, the hydrolysis of amylopectin is incomplete, and large amounts of dextrins containing 30 or more glucose units are detected in the jejunum.[6] This is in direct contrast to infants at the end of the first year of life, where amylopectin is rapidly hydrolyzed into glucose, maltose, maltotriose, and branch dextrins.[6] Starch fed as 18% of caloric intake was not completely digested by some infants. A substantially greater proportion of infants fed in this manner weighed below the tenth percentile.[1]

The effects of MFS on trace nutrient bioavailability has received limited attention. In animal experiments, iron retention in rats was adversely affected by cooked modified starches.[7] The information available has been obtained in either in vitro experiments or experiments in the rat, and it has to be interpreted with caution. The lack of an adequate animal infant model for evaluating trace element bioavailability further complicates extrapolation from the limited data. Toxicological considerations in rats fed MFS are of primary concern. Feeding rats with a diet of 30% MFS for two years resulted in renal lesions, such as pelvic nephrocalcinosis, hydronephrosis, hyperplasia of pelvic epithelium, and the finding of parasites considered to be Trichosomoides crassicauda.[8] In the past, propylene oxide and epichlorohydrine were used for preparation of MFSs.

Because these chemicals are known to be carcinogenic or mutagenic,[9] the committee on safety of MFSs has recommended that MFS epichlorohydrine or propylene oxide should not be used in infant foods until additional data evaluating their safety becomes available.[2]

In animal models, cecal enlargement, parathyroid hyperplasia, giant multinucleated hepatocytes, periarteritis affecting small and middle-sized arteries in the pancreas, and papillomatosis of malpighian mucosa of the rumen have been observed with diets of high content of MFS.[1] Diarrheal symptoms have been observed in rats in various feeding studies, especially when the starch provided 50% or more of the diet. The importance of these observations to infants is difficult to evaluate because the studies were done on mature animals.[10]

Acute gastroenteritis may result in mucosal injury of the small intestine that might last from several days to a few months and may further affect the ability of the infant to tolerate starch feeding. These considerations are even more important for infants in developing countries where, because of recurrent GI infections and malnutrition, the use of MFSs might be contraindicated. Since infants younger than 6 months of age may have a limited ability to digest modified and unmodified starches, it is recommended that total dietary-starch use be limited for this age group.

Recent studies suggest that the inability to digest starch may interfere with the absorption of other nutrients. Therefore, there is an urgent need for additional data in this area. The effect of MFS at specific ages on digestion and element bioavailability needs to be elucidated. Careful animal studies should be performed to evaluate toxicological, mutagenic, and carcinogenic effects of the chemicals used to modify the starch. In light of these considerations, current practices with MFSs should be evaluated and their indiscriminate use in the first six months of life should be discouraged until further information is available.

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Comparison of Human Rotavirus Disease in Tropical and Temperate Settings

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• Human rotaviruses (HRV) are a common cause of acute nonbacterial gastroenteritis in pediatric patients. A prospective study of HRV disease in a temperate (Dallas) and a tropical (San Jose, Costa Rica) setting demonstrated differences in seasonal distribution. In both locales, HRV accounted for 50% to 60% of acute nonbacterial gastroenteritis episodes from December through February; this period corresponded to the cooler months of winter in Dallas and to the dry season in San Jose. During the rest of the observation year, the virus was not recovered from any Dallas patients, but was found in 30% to 40% of Costa Rican patients in every month but May. Signs, symptoms, and laboratory values suggest the small bowel as the major site of pathophysiology; mucosal disruption may occur in some cases.

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The recent application of electron microscopic techniques to the study of fecal viruses[1] has resulted in the recognition of a close association between the excretion of human rotaviruses (HRV) and the acute nonbacterial gastroenteritis of infancy commonly known as "winter vomiting disease."[2-5] Rotaviruses are characterized by a double-stranded RNA core surrounded by a distinctive double-layered capsid with an outside diameter of 70 nm. These agents were formerly considered as solely veterinary and plant pathogens.[6,7] They have now been confirmed as important causes of winter season epidemics of acute nonbacterial gastroenteritis from many areas of the world.[8-12] With the exception of the recent report from India by Maiya et al,[13] the seasonal distribution of HRV excretion has not been prospectively studied in a tropical setting that has no winter season, but only rainy and dry seasons. In the latter study of 50 patients during a one-year period, HRV was recovered from 13 patients (26%) during the cooler months of July through December. No patients could be studied from January through March and no HRV was recovered from April through May. None of the 30 control patients were found to be excreting HRVs.

We have compared the seasonal distribution of HRV disease in a temperate (Dallas) and tropical area (San Jose, Costa Rica).

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METHODS

A number of infants and children younger than 8 years of age who were seen in the outpatient department or were hospitalized for nonspecific acute gastroenteritis were selected for study. Patients with clinical features suggestive of a bacterial pathogen, such as high fever or bloody stools, were excluded. Informed, written parental consent was obtained. Acute serum and stool specimens were obtained from patients and, whenever possible, convalescent specimens were obtained seven to 14 days later. Similar samples were collected from an age-matched control subject in many instances; these patients and their families had not had acute gastroenteritis in the previous week and were being treated for ailments unrelated to the gastrointestinal (GI) tract (fractures, respiratory and urinary tract infections, etc).

The stools were examined for polymorphonuclear leukocytes (PMNs) with Wright and methylene blue stains.[14] Standard bacteriologic techniques were used to identify salmonellae, shigellae, and enteropathogenic serotypes of *Escherichia coli* (EPEC). Samples were stored at −70 °C prior to testing with the exception of the Costa Rican stools and all the serum samples that underwent transient thawing during air shipment on dry ice. Stools were examined for the presence of HRVs, adenoviruses, and enteroviruses by electron microscopy using a modification of previously published methods.[15,16] A 10% (weight/volume) stool suspension in sterile water was homogenized in a blender and clarified of lipid by extraction with equal volumes of trichlorotrifluroethane (Genesolv). Large debris and bacteria were removed by centrifugation at 6,000 RPM for 30 minutes. A drop of the supernatant was allowed to dry on the surface of a noble agar block (pseudoreplica technique) and was then covered by a 0.25%-enamel film (Formvar). The film was then floated off the agar and stained for three minutes in a lake of 3% phosphotungstic acid and examined on a 400-mesh copper grid in a transmission electron microscope.

Human rotaviruses were identified by their characteristic double-capsid morphology and size of 70 nm (Fig 1). Adenoviruses and enteroviruses were also identified morphologically. Serums were assayed for complement fixing HRV antibodies using Nebraska calf diarrhea virus (NCDV) and "O" agent as antigens according to previously described methods.[17] Previous exposure to HRV was considered present when acute serums were positive in a titer of 1:16 or greater; a fourfold or greater rise in titer was considered diagnostic of recent HRV infection.

RESULTS

One hundred thirty patients with diarrhea in San Jose and 57 patients with diarrhea and 23 control patients in Dallas were studied. Human rotaviruses were detected in 16 Dallas patients (28%) and in 49 Costa Rican patients (38%). One control patient (4%) was found to be excreting HRV. This 9-year-old boy had been hospitalized with a fractured femur for ten days. He had no known family or hospital exposure to gastroenteritis. Several hours after the first stool sample was obtained vomiting and watery diarrhea developed. The initial stool sample contained only one to two

HRVs per grid square, but a subsequent diarrheal stool sample contained large numbers of HRVs. Mata et al[18] conducted a similar study of Costa Rican patients hospitalized for greater than 24 hours during the period January 1976, through January 1977; they found only two of 45 control patients (4%) to be asymptomatic excretors of HRVs. No data on nosocomial acquisition or subsequent development of GI disease are available on these patients.

Clinical features are given in Table 1. In Dallas, the HRV-positive patients with diarrhea were afebrile and all had vomiting. The stools were watery and without blood, but mucus was present in 50% and PMNs were present in 31%. Severe dehydration was present in 44%, and 38% were hospitalized. Seventy-five percent had respiratory tract symptoms. The mean total duration of illness was one week with a range of two to ten days. The HRV-negative patients were less likely to have vomiting, had fewer stools, less severe dehydration, were less likely to be hospitalized, less likely to have respiratory tract symptoms, and had a more prolonged course of illness. The isolation rates of EPEC of 6.3% in HRV patients and 4.3% in controls are not substantially different and are comparable to the asymptomatic carrier rate of 5.8% previously reported in a larger number of infants studied in Dallas.[19]

In San Jose, the characteristics of HRV-positive patients were similar to those of Dallas patients except that they were more likely to have fever and only 20% had severe dehydration. Only 8% of the patients were hospitalized for more than 24 hours in San Jose, but all others were held for variable periods in an outpatient facility for observation and rehydration. *Shigella*, *Salmonella*, and EPEC were more frequently present in Costa Rican children, and isolation rates were comparable in HRV-positive and negative patients. Follow-up of 27 of the HRV-positive patients in Dallas after clinical resolution of the diarrhea disclosed only one (3.7%) still excreting HRVs 12 days after onset of illness.

Figure 2 and 3 show the electron microscopic studies. In Dallas, the detection of HRVs correlated well with the peak winter periods of acute gastroenteritis requiring admission to Parkland Memorial Hospital. Human rotaviruses were absent from April through September 1976. Unfortunately, no participants for the study could be enlisted during October and November 1977, at the beginning of a clinically typical epidemic of nonbacterial winter vomiting disease. Although a small number of patients were noted to excrete enteroviruses and adenoviruses during the spring, these agents did not seem to account for the minor peak in admissions for diarrhea noted from June through August 1976.

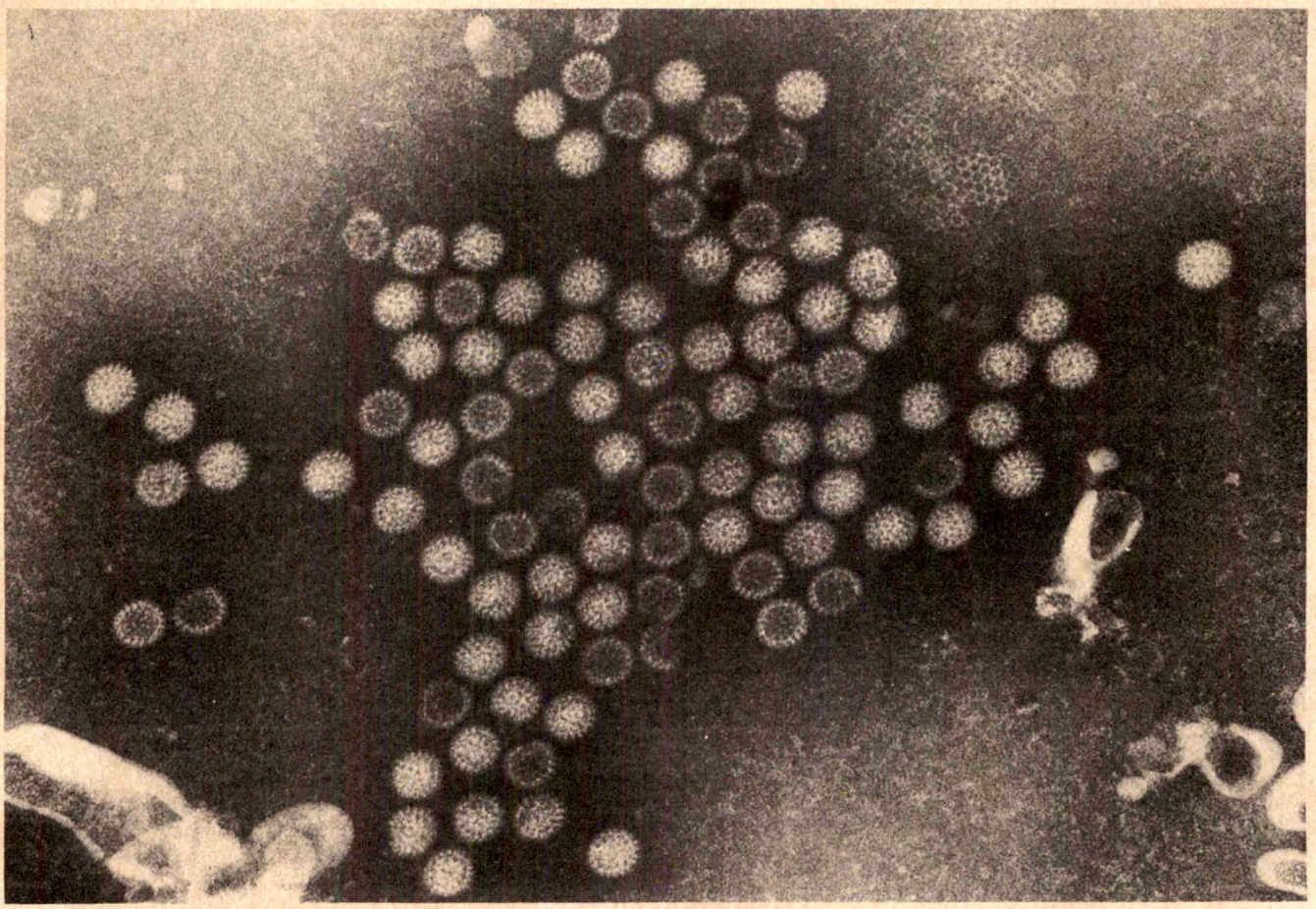


Fig 1.—Typical human rotaviruses as visualized in stools of patients with gastroenteritis, 3% phosphotungstic acid; (original magnification ×25,000).

Table 1.—Clinical Features of Study Patients

	Dallas			San Jose, Costa Rica	
	HRV-Positive*	HRV-Negative	Control	HRV-Positive	HRV-Negative
No. of patients Age, mo (range)	16 7.8 (2-17)	41 9.9 (1-48)	23 7.7 (2-19)	49 7.3 (1-17)	81 6.2 (1-36)
Patients with fever, %					
None	100	88	26	49	63
to 38°C	...	5	17	27	15
> 38°C	...	7	57	24	22
Patients with vomiting, % (Mean of episodes 24 hr at onset of illness)	100 (4.4)	66 (2.6)	0 (0)	90 (6.3)	89 (4.5)
Mean of diarrheal stools/24 hr at onset of illness	9	6.8	0	8.6	7.8
Character of stools, %					
Watery	100	100	4	100	100
Yellow	63	51	9	39	41
Green	50	44	17	43	38
Brown	0	22	70	18	21
Bloody	0	7	0	NR†	NR
Mucous	50	59	0	NR	NR
Stool polymorphonuclear lekocytes	31	24	4	18	12
Patients with dehydration, %					
< 5% dehydration	56	95	0	80	75
> 10% dehydration	44	5	...	20	25
Patients with peripheral polymorphonuclear leukocytes/bands > 10,000/1,000 per cu mm, %	7/19	3/10	13/35	NR	NR
Patients with bacterial pathogens, %					
Shigella	0	5	0	10	6
Salmonella	0	0	0	6	7
Enteropathogenic *Escherichia coli*	6	5	4	16	12
Total	**6**	**10**	**4**	**32**	**25**
Patients with respiratory symptoms, %	75	49	39	NR	NR
Mean duration of illness before being seen, days	3.2	4.0	4.6	3.5	3.9
Mean total duration of illness, days (range)	6.8 (2-10)	9.0 (3-16)	...	5.6 (3-12)	9.0 (4-25)

*HRV indicates human rotavirus.
†NR indicates not recorded.

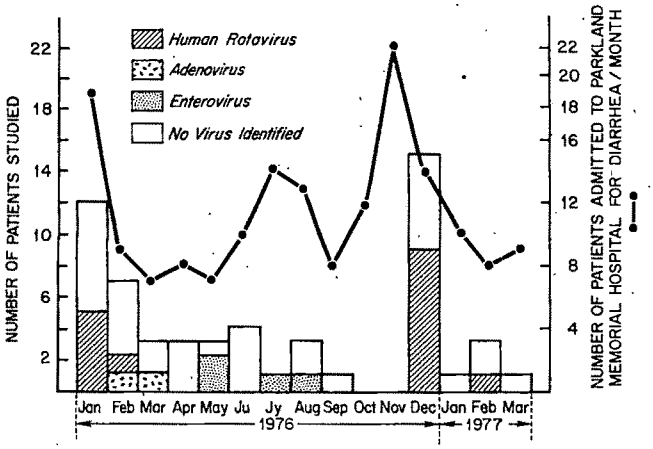


Fig 2.—Identification of fecal viruses by electron microscopic morphology, Dallas.

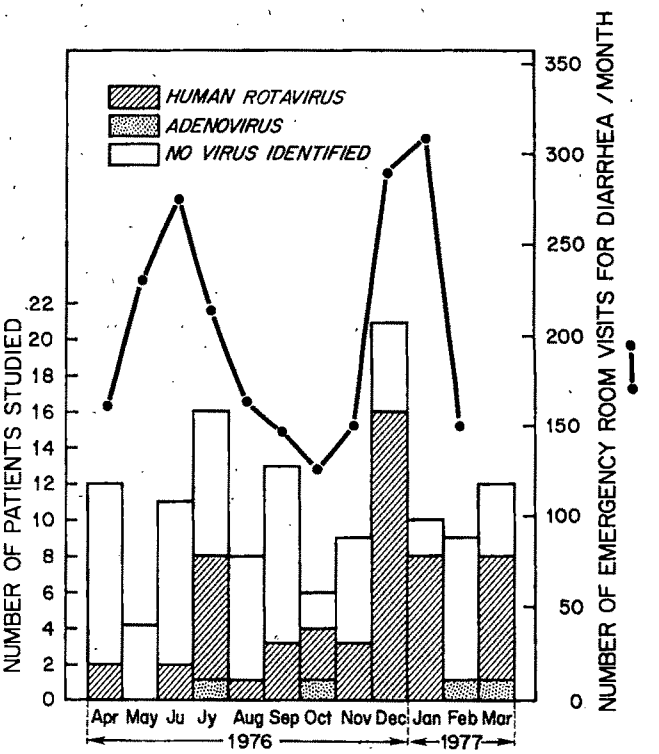


Fig 3.—Identification of fecal viruses by electron microscopic morphology, San Jose.

Costa Rican specimens collected from January through March 1976, were irreparably damaged during a power failure. In San Jose, a substantial increase in HRV excretion correlated with a peak in emergency room visits for diarrhea noted at the beginning of the dry season in December 1976, and January 1977. Human rotaviruses were noted in a lower percentage of patients in every month during the year's observation period, except May 1976. A secondary peak in emergency room visits for diarrhea in May through July 1976, was not well correlated with any viral agent as detected by electron microscopy nor with bacterial pathogens.

In San Jose, the mean daily temperature is constant each month at 20 °C throughout the year and, even in the dry season from December through March, the relative humidity averages 75% to 80% (Fig 4). In Dallas, the mean monthly relative humidity fluctuates between 25% and 60%, roughly in relation to the number of days of rain and the mean daily temperatures average greater than 27 °C in midsummer and drops to 10 °C or lower in the midwinter months (Fig 5). In both locales, HRV disease does not correlate well with any of these three climatic factors, although there is a tendency for its occurrence in the months with the fewest days of rain.

Figure 6 illustrates the seasonal variations of HRV excretion. In both Dallas and San Jose, there is a peak in excretion (50% to 60% of acute gastroenteritis patients) from December through February. In Dallas, the virus is then absent until it reemerges in late fall, whereas in San Jose it continues to be excreted by 30% to 40% of patients throughout the remainder of the year.

Serologic responses of study patients are given in Table 2. Patients with HRV-positive gastroenteritis were significantly ($P = .001$) more likely to demonstrate a fourfold or greater titer increase than HRV-negative patients with diarrhea.

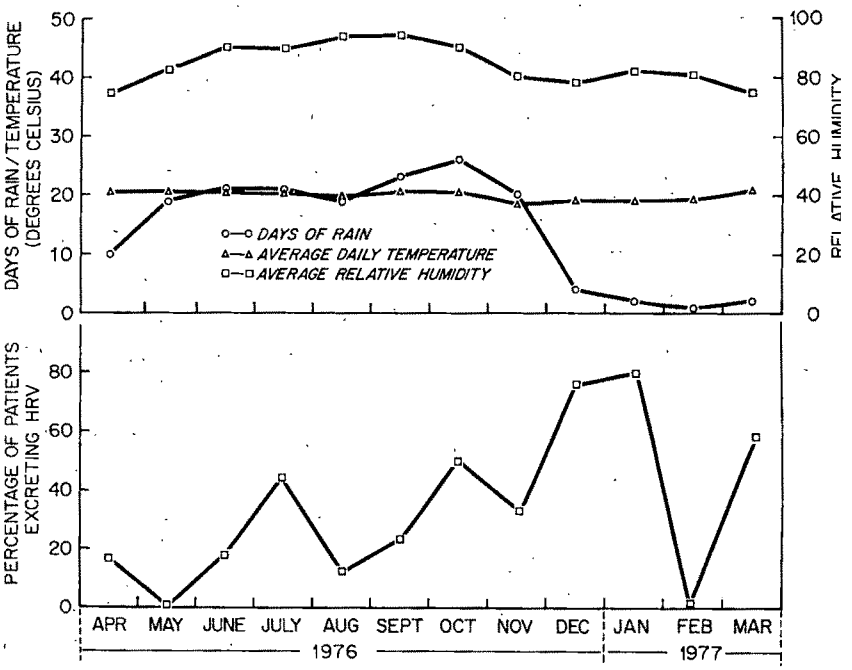


Fig 4.—Relation of human rotavirus excretion to climatologic variables, San Jose.

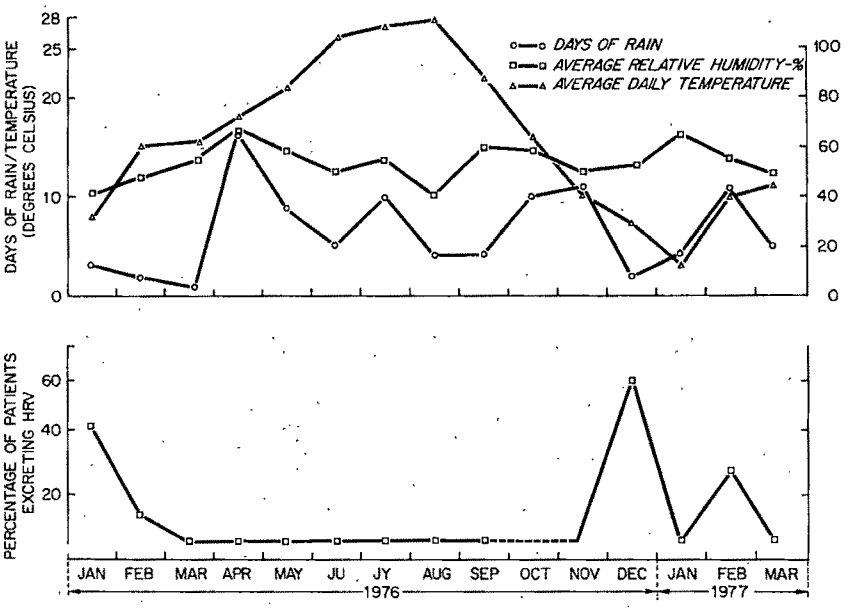


Fig 5.—Relation of human rotavirus excretion to climatologic variables, Dallas.

COMMENT

Many previous authors investigating the role of bacteria, viruses, and parasites in the cause of acute gastroenteritis of infants and children have been unable to assign a pathogen in as many as 40% to 60% of the cases.[20-23] Recent advances in two areas of investigation have led to a considerable reduction in the number of cases without an identifiable causal agent. The first advance was the recognition that diarrhea may be caused by enterotoxigenic and enteroinvasive strains of *E coli* that are often antigenically unrelated to the classic enteropathogenic serotypes.[24,25] The second advance involved the description of outbreaks of acu nonbacterial gastroenteritis due Norwalk and related agents.[26,27] The viruses are unique in that stools acutely ill patients contain up to 1 infectious particles per gram, whi are not recoverable by routine tissu culture methods.

Proof of infectivity was obtain only after in vivo serial passage e periments and replication in elabora fetal organ cultures. Reasoning th other important viral gastroenteri

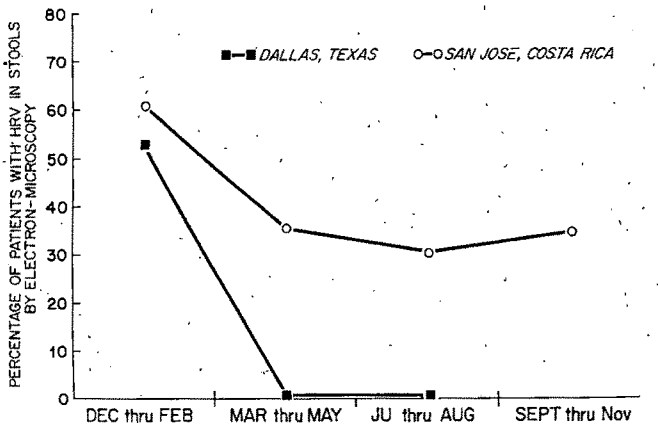


Fig 6.—Seasonal variation in human rotavirus excretion in tropical (San Jose) and temperate (Dallas) climates.

Table 2.—Complement Fixation Serologic Responses of Study Patients Using Nebraska Calf Diarrhea Virus and "O" Agent as Antigen*

Patients	Acute Serum Only: Titer ≥ 1:16 (%)	Acute and Convalescent Serums %: Acute ≥ 1:16	Acute and Convalescent Serums %: ≥ 4-Fold Increase in Titer
Control patients, Dallas	2/9 (22)	0/8 (0)	2/9 (22)
Patients with acute gastroenteritis with human rotavirus in stool			
Dallas	2/9 (22)	1/4 (25)	2/4 (50)
San Jose	2/32 (6)	0/10 (0)	6/10 (60)
Patients with acute gastroenteritis without human rotavirus in stool			
Dallas	1/14 (7)	4/18 (22.2)	1/18 (6)
San Jose	5/37 (14)	2/11 (18.2)	1/11 (9)

*Number of patients who tested positive/number of patients tested.

agents might have previously been missed by routine tissue culture techniques, electron microscopists have recently described in stools a variety of virus-like particles associated with acute gastroenteritis.[28-37] Although most of these particles are awaiting full evaluation as verified causes of acute gastroenteritis, accumulated data on HRVs indicate that they are an important cause of pediatric acute nonbacterial gastroenteritis in many areas of the world.[4-7,38-42] They were missed in earlier studies of viral gastroenteritis because of their failure to replicate in routine tissue culture systems.[43-47]

This study confirms the strong association between HRV excretion and pediatric gastroenteritis and adds the southwestern United States and Central America to the growing list of locations where as many as 60% of patients with winter vomiting disease have HRVs as their only identifiable pathogen. The observations in this study of specific serologic response and clearance of HRVs coincident with resolution of gastroenteritis, the rarity of HRV excretion by asymptomatic control patients, and the occurrence of apparent nosocomial infection support the conclusion of others[10,48-50] that HRV is an important cause of gastroenteritis in infants and children.

The pathophysiology of HRV-mediated gastroenteritis is currently unknown. The clinical features of vomiting, copious watery diarrhea without blood, and the lack of fever suggest that the small bowel is the major site of involvement.[51] Recovery of HRVs from small-bowel aspirates and biopsies,[52,53] transient depression of D-xylose absorption during HRV excretion,[54] and proof of this site of action for Norwalk agent in human volunteer studies[55] make this an attractive hypothesis. Studies of viral gastroenteritis in animals have documented primarily small-bowel involvement, but colonic involvement has also been noted.[56-57] Many of the clinical features of HRV-mediated acute gastroenteritis are similar to the small bowel syndrome produced by the enterotoxins of *Vibrio cholerae* and *E coli*[51] in which net fluid secretion occurs without mucosal disruption. The observation of stool PMNs in 31% of our HRV-excreting patients and the increased peripheral band form counts in 19% raise the possibility that mucosal disruption of the small bowel and/or colon may occur in some patients with HRV infection.[14]

In both Dallas and San Jose, an increase in the incidence of acute nonbacterial gastroenteritis occurs during the period October through February. In Dallas, as in other temperate climates, these outbreaks have been called winter vomiting disease as their occurrence correlates well with the onset of cooler weather. This relationship to temperature was noted in Australia where cooler weather and HRV-positive gastroenteritis are maximal between May through September.[8] San Jose is a tropical environment without considerable variation in temperature or relative humidity throughout the year of study; however, there was a peak of cases in the dry season. In Dallas, the period of peak HRV disease also was in the cooler months with the fewest days of rain. These data suggest that the periodic epidemics of HRV gastroenteritis are not solely a function of seasonal variation in environmental temperature. The controlling factor(s) underlying the cyclic variation in excretion of these enteric viruses remains unknown.

The virtual disappearance of HRVs from Dallas patients from March through September along with the apparent absence of an asymptomatic carrier state[8] raise the interesting question as to the mode of viral persistence from one winter season to the next. One unexamined possibility is that minimally symptomatic adults may serve as the host allowing viral persistence in the temperate zone populations.[58,59] It is also possible that asymptomatic carriers exist, but the quantity of virus in the stool is small and escapes detection by electron microscopy. Virus may persist in the environment in nonhuman reservoirs. In striking contrast, is the observation

in tropical San Jose of HRV excretion throughout the year in at least 30% to 40% of gastroenteritis patients during nonepidemic periods. This higher rate of HRV excretion in Costa Rica could represent a basic difference in epidemiology or in host factors between Dallas and San Jose or could merely be due to a greater exposure to a wide variety of enteric pathogens as reflected by the higher percentage of Costa Ricans with bacterial pathogens.

This prospective longitudinal study has confirmed the importance of HRV as a cause of pediatric gastroenteritis in the southwest United States and Central America. Comparisons of the disease in a temperate and a tropical setting point out that a unifying epidemiologic concept is not yet ava able.

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Jaundice and Breast-Feeding Among Alaskan Eskimo Newborns

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• The course, incidence, and severity of neonatal jaundice was studied in 95 Alaskan Eskimo infants. Breast-fed infants had higher bilirubin concentrations than bottle-fed babies. Both groups experienced high bilirubin levels, similar to those previously reported in Navajo and Oriental infants but greater than those observed in whites and blacks. A marked capacity to inhibit hepatic glucuronyl transferase was observed in breast-milk specimens but only partly accounted for the bilirubin differences between breast-fed and bottle-fed Eskimo infants. These data suggest that in some racial groups predisposed to neonatal jaundice, feeding practices significantly alter the course and severity of hyperbilirubinemia.

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Several reports[1-7] have suggested a relationship between race and the intensity of neonatal jaundice. Orientals and American Indians appear to have higher serum concentrations of unconjugated bilirubin in the newborn period than do whites or blacks. Moreover, the usual pattern of jaundice, with a peak bilirubin level at day 3 or 4 and a subsequently rapid decline, is not characteristic of at least one group of previously studied American natives, the Navajo.[7] The higher levels of bilirubin observed in Orientals and American Indians have not been completely accounted for by differences in birth weight, feeding practices, or the incidence of isoimmunization. The study in Navajos[7] disclosed an important effect of breast milk on inhibiting the bilirubin conjugating system when compared to that of milk from white and black populations. However, this did not entirely account for the racial differences noted, as bottle-fed Navajo infants also experienced high bilirubin concentrations.

Recently, we have observed a similar pattern of jaundice and neonatal feeding practices among Alaskan Yupik Eskimo newborns. The present study describes this clinical experience and offers a partial explanation of the mechanism that may be involved in this neonatal hyperbilirubinemia.

SUBJECTS AND METHODS

One hundred seventeen consecutive live births between Jan 1 and June 15, 1975, at the Public Health Service Alaska Native Hospital, Bethel, were monitored. Ninety-five infants met the study criteria of a full-term gestation by physical examination and a birth weight between 2,500 and 4,500 gm. A 50% or more Alaskan native heritage (Yupik Eskimo), as determined by parental history, was also required to be included as a study subject. Infants with conditions predisposing to jaundice, such as hemolytic disease, sepsis, birth trauma, or antenatal administration of drugs known to interfere with bilirubin metabolism, were excluded from the study.

All infants were given natural vitamin K intramuscularly in the delivery room. The decision to breast-feed or bottle-feed was made by the mother. Breast-fed infants were given supplementary glucose water, except for two whose mothers had postpartum tubal ligation. In these two instances, commercial formula was given for the first 48 hours and thereafter breast-feeding was begun. There were 68 breast-fed and 27 bottle-fed babies in the study.

Samples of cord blood were obtained from 88 infants. Subsequently, capillary blood specimens were obtained each day the infants remained in the hospital, up to five days. The total serum bilirubin and hematocrit values were determined on all samples. Bilirubin concentrations were determined at the Bethel Hospital by standardized techniques utilizing the method of Malloy and Evelyn.[8] In addition, 49 cord sera, 33 aliquots of breast milk obtained on the second or third postpartum day, 35 maternal urine samples obtained at the same time, and 38 maternal serum samples

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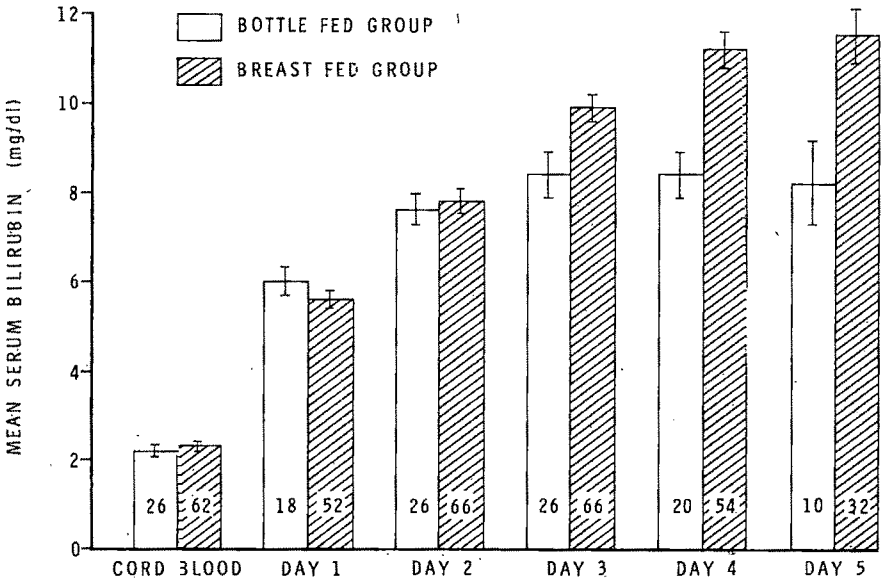


Fig 1.—Serum bilirubin concentrations in cord blood and during first five days of life in Alaskan native infants. Height of each bar depicts mean total bilirubin concentration; cross bars, ± 1 SE. Digits within each bar represent number of infants sampled on that day. Statistically significant differences between groups exist on days 4 and 5 ($P < .01$).

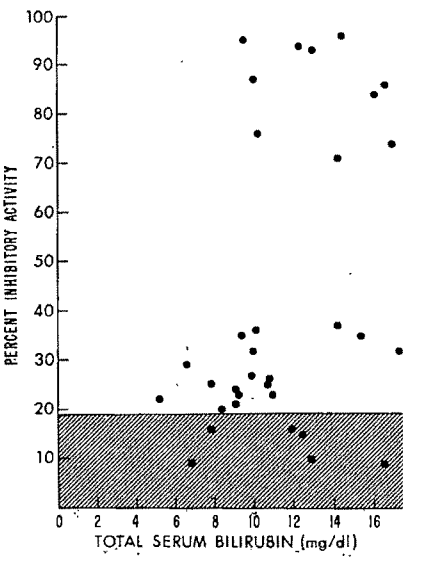


Fig 2.—Peak serum bilirubin levels in 3 native Alaskan infants, plotted agains degree of inhibition of bilirubin glucuron transferase activity by their own mother milk. Inhibitory activity of 20% or greater considered significant.

Racial Origins and Their Relationship to Neonatal Bilirubin Concentrations and Feeding Practices

Source	Racial Group	Feeding Practice	No. of Patients	Maximum Serum Bilirubin, mg/dl	Age of Patients, Days
Davidson et al[11]	White & black	Not stated	106	6.7	3-4
Dahms et al[12]	White	Bottle	86	5.9	2-3
	White	Breast	113	6.9	2-3
Brown and Boon[4]	White	Mixed	36	4.4	2-3
	Indian	Breast	25	9.6	4
	Malay	Breast	92	9.7	4
	Chinese	Mixed	162	11.6	4
Yeung et al[13]	Chinese	Not stated	45	12.5	4-5
Yamauchi et al unpublished data	Japanese	Breast	25	13.4	7
Trygstad and McCracken[5]	American Indian(Sioux)	Not stated	31	11.7	4
Saland et al[7]	American Indian(Navajo)	Bottle	3	10.0	4
	American Indian(Navajo)	Breast	13	14.5	4
	Black	Bottle	35	5.8	2-3
Present study	Eskimo	Bottle	26	8.4	3-4
		Breast	33	11.5	5

obtained on the first postpartum day were frozen and stored in the dark for later analysis. The stored maternal and cord sera, breast milk, and maternal urine samples were transported frozen to New York and assayed for the presence of inhibitory activity of bilirubin glucuronyl transferase (International Enzyme Commission Code EC 2.4.1.17) as previously reported,[7] utilizing the methods of Black and Billing[9] and a modification of the methods of DeLeon and associates.[10] This modification included the addition of 2% digitonin in 0.154 M KCl added to an 8% rat liver homogenate in a 1:1 dilution just prior to the addition of 0.1 ml of uridine diphosphate glucuronic acid (6.6×10^{-2}).

RESULTS

Of the 95 infants, 77 were full-blooded or seven-eighths Yupik Eskimo, 17 were half or three-quarters Yupik Eskimo-white, and one was mixed Yupik Eskimo-Athabascan.

The mean serum bilirubin concentrations of the infants for the firs five days of life are shown in Fig Using Student's t test, the difference between breast-fed and bottle-fe infants were significant ($P < .01$) o days 4 and 5. Both groups, however had considerably higher bilirubin lev els than had been noted for whites an blacks, but similar to those reporte previously for American Indian an Oriental populations. The Table sum marizes comparative data from th

literature on racial origins, total serum bilirubin levels, and feeding practices.

The average birth weight for the study group was 3,458 gm. Bottle-fed infants lost an average of 89 gm, while breast-fed infants lost an average of 177 gm, during the first five days of life. Among breast-fed infants, no significant correlation was observed between weight loss and the peak bilirubin level. Moreover, there was no significant correlation between birth weight and peak bilirubin level.

Thirty-three specimens of breast milk were assayed for in vitro ability to inhibit hepatic bilirubin glucuronyl transferase activity.[14] The mean percent inhibition for all Alaskan native breast milk was 42%. The inhibitory activity of each sample is plotted against the corresponding serum bilirubin concentration in Fig 2. The presence of inhibitory activity of less than 20% is considered a nonspecific finding of the assay method and is not significant. This was noted in six milk specimens, while 27 demonstrated the presence of significant inhibition. The ten infants whose mothers had breast milk inhibition exceeding 71% all had peak bilirubin levels over 9.4 mg/dl, and seven had levels over 12.0 mg/dl. The other 23 milk specimens had inhibition of less than 40%, and only six infants consuming this milk had bilirubin levels over 12.0 mg/dl. Thus, high breast milk inhibitory capacities seemed to be associated with high peak serum bilirubin concentrations in the newborns.

Similar in vitro assays were performed to determine the presence of inhibitory activity on 49 cord sera, 35 maternal urine specimens, and 38 maternal sera from 50 of the mother and infant pairs. All but five of these 122 individual determinations for cord sera (three) and maternal urine (two) were below the level of inhibitory activity believed needed to produce significant unconjugated hyperbilirubinemia, which suggests there was no placental transmission of a maternal inhibitor substance. None of the maternal serum specimens displayed inhibitory activity.

COMMENT

Substantial differences exist among races regarding the incidence, severity, and course of hyperbilirubinemia in the newborn. Higher bilirubin levels occur among infants of Oriental and American native descent than among white or black infants. In the present study we have extended these observations to the Alaskan Eskimo infant. As a group, the Eskimo infants experienced bilirubin levels higher than have generally been found in whites and blacks. Additionally, among the Eskimos, serum bilirubin levels on days 4 and 5 were significantly high in breast-fed infants compared to those who were bottle fed. Moreover, the breast-fed infants did not show an early plateau or decline in serum bilirubin level as did the bottle-fed infants, or as do most white infants. Birth weight, early neonatal weight loss, and red blood cell incompatibility were not important factors in the study group. Breast milk specimens of the Eskimo mothers possessed impressive capacities to inhibit bilirubin glucuronidation in vitro. While no linear correlation was found between inhibition in the mothers' milk and serum bilirubin level in the newborn, none of the infants consuming milk with high inhibitory capacities had peak bilirubin values less than 9.0 and most were between 12.0 and 17.0 mg/dl.

The mechanism of "physiologic" jaundice in the newborn is not yet clearly understood. Delayed glucuronidation, increased red blood cell volume, the role of Y and Z proteins in the uptake and intracellular transport of bilirubin, as well as other factors in hepatocellular uptake and the enterohepatic recirculation of bilirubin, all may play a role in some of the racial differences that have been described.[15]

It is likely that hyperbilirubinemia and its prolonged course among breast-fed Eskimo infants can be partly attributed to breast milk-transmitted inhibitor substances. Other genetic factors must also exist to account for the distinct racial differences observed among bottle-fed and breast-fed infants. Among those races with a genetic proclivity to neonatal hyperbilirubinemia, breast-feeding practices probably play an important role in potentiating the phenomenon.

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Obesity in Urban Black Adolescents of High and Low Relative Weight at 1 Year of Age

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• The prevalence of obesity was determined in 798 9 to 15-year-old Philadelphia subjects who had either a high (+1 SD) or a low (—1 SD) relative weight at 1 year of age. During the adolescent years, obesity was assessed by the triceps skin-fold thickness and by the relative weight, using national reference standards from the US Health Examination Survey. The prevalence of obesity for the high relative weight group at 1 year of age was three to four times higher than in the low relative weight group at 1 year of age. Compared with all urban youth of this age range, regardless of their status at 1 year of age, it is estimated that the risk ratio associated with a high relative weight at 1 year of age is approximately 1.6.

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In recent years, the study of the etiology of obesity has increasingly come to focus on the role of infant growth as an agent. Several studies have indicated the persistence of infant "obesity" into the childhood years[1-4] while the research into adipose cell hyperplasia and hypertrophy[5,6] has provided a physiological basis for this persistence.

However, despite the increasing, and frequently contradictory, body of knowledge, there is little systematic information relating infant growth to obesity during the adolescent years. For this reason, we present the data in this article, taken from a prospective study of adolescents who at 1 year of age were in the highest or lowest percentiles of weight for length. The results will add to our knowledge of the relative risk of obesity beyond childhood associated with rapid weight gain during the first year of life.

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MATERIALS AND METHODS

The study population consisted of persons whose mothers participated in the Philadelphia component of the National Perinatal Collaborative Study; the study was restricted to black youths since they make up the greatest proportion of the component. A total of 8,470 black infants were registered between 1960 and 1965, of whom 6,600 were followed up at 4, 12, 48, and 72 months of age. From this follow-up group, the weight at 12 months of age was statistically regressed on body length; those individuals at the two extremes of the distribution were selected for the study. The selection process moved from the extremes toward the center, care being given to having the limit remaining greater than and less than 1 SD and to maintaining an adequate number of subjects in each age group. A total of 9 persons were selected, of whom 798 (84 were actually examined. The subjects w between 9 and 15 years of age and all w residents of Philadelphia.

The study was designed to compare t obesity status of adolescents who, at 1 y of age, had either a high (greater tha SD) or a low (less than 1 SD) relat weight, ie, weight for length. These grou are referred to, as RW1+ and RW1 respectively. In the absence of a m direct measure of body fatness at 1 year age, we have determined the relationsl between skin-fold thickness and relati weight of infants of a similar populati though the infants were measured in 19 In 100 black infants, at 9 to 24 months age, the correlation between relati weight and the sum of five skin fol (triceps, biceps, subscapular, abdomin and suprailiac) was +0.72, suggesting th in our sample, relative weight is an acce able measure of infant fatness.

Table 1.—Prevalence of Obesity in Boys, as Judged by Triceps Skin Fold and Relative Weight, by Age, Sex, and Relative Weight at 1 Year of Age

Age Group, yr	No. RW1—	No. RW1+	% RW1—	% RW1+
Triceps Skin Fold				
9	5/31*	11/20	16	55
10	4/29	21/46	14	46
11	9/34	13/31	27	42
12	4/40	15/41	10	37
13	3/31	11/32	10	34
14	3/35	12/29	9	41
15	0/3	1/6	0	17
Total	**28/203**	**84/205**	14	42
Relative Weight				
9	1/31	7/20	3	35
10	2/29	8/46	7	17
11	3/34	7/31	9	23
12	2/40	12/41	5	29
13	3/31	8/32	10	25
14	3/35	9/29	9	31
15	0/3	2/6	0	33
Total	**14/203**	**53/205**	7	26

*Number judged obese/number examined.

Table 2.—Prevalence of Obesity in Girls, as Judged by Triceps Skin Fold, and Relative Weight, by Age, Sex, and Relative Weight at 1 Year of Age

Age Group, yr	No.		%	
	RW1−	RW1+	RW1−	RW1+
Triceps Skin Fold				
9	4/22*	8/14	18	57
10	2/34	18/37	6	49
11	3/33	11/29	9	38
12	4/34	6/30	12	20
13	4/30	9/44	13	21
14	5/39	7/31	13	23
15	1/3	3/10	33	30
Total	**23/195**	**62/195**	12	32
Relative Weight				
9	1/22	5/14	5	36
10	3/34	18/37	9	49
11	2/33	13/29	6	45
12	4/34	9/30	12	30
13	4/30	17/44	13	39
14	4/39	9/31	10	29
15	0/3	2/10	0	20
Total	**18/195**	**73/195**	9	37

*Number judged obese/number examined.

For adolescence we have defined obesity in two ways, using a separate analysis for each. First, we have categorized as obese any person whose triceps skin fold fell above the 90th percentile value for black youths of the same age and sex of the national probability sample examined by the US Health Examination Survey.[7,8] These data are widely used as reference standards and have provided the first such national standards for height and weight.[9]

Second, we have categorized as obese any person whose relative weight was 120% or greater. Using the Health Examination Survey data,[10,11] the predicted weight for each subject was calculated from the regression of the median weight for height, by age and sex, for the Health Examination Survey subjects. The relative weight of that person was then calculated as: predicted weight/actual weight × 100.

RESULTS

Tables 1 and 2 give the number of youths of each sex and relative weight in each age group. Adequate numbers of subjects were available for analysis in every group except for those 15 years old, where there were only 22 persons in all.

Tables 1 and 2 also give the number and percentage of subjects of each sex, age, and RW1 group judged to be obese by the thickness of the triceps skin fold and by the relative weight. Clearly the percentage of obesity is consistently higher among RW1+ youth. For all age groups combined, 41% of RW1+ boys and 32% of RW1+ girls were obese according to triceps skin-fold thickness. For RW1− subjects, the corresponding percentages were 14% and 12%, respectively. In other words, the ratio of obesity in RW1+ adolescents to that in RW1− adolescents is almost 3:1, regardless of gender.

When the relative weight is used as the measure of obesity, the prevalence tends to be somewhat less than when the triceps skin fold is used as the measure of obesity. However, the patterns remain and in fact, the difference between RW1+ and RW1− subjects is accentuated. The ratio of obesity percentage in RW1+ to RW1− youths is approximately 4:1 in both boys and girls.

COMMENT

Previous research into the role of infant growth in later obesity suggests that the two are related. Forbes[12] was among the first to identify a subgroup of obese adolescents who had been overweight since infancy and who displayed increased lean body mass and advanced bone age. He suggested that the prognosis for lasting weight reduction among such persons was poorer than among those whose obesity was not associated with other growth variables.

Short-term studies have shown that overweight infants tend to remain overweight in childhood. Sveger et al[1] found that 50% of 213 infants classed as obese were still obese between 1½ and 2½ years. Huenemann[2] also found rapid weight gain between birth and 6 months of age to be associated with childhood obesity, while Mack and Ipsen[3], analyzing data from the National Collaborative Study, found a persistence of a high relative weight at 1 year of age among those 4 years old.

For middle and late childhood, the picture is less clear. Fisch et al[13] analyzed the relative birth weights of Minnesota infants of the Collaborative Survey and found a movement toward a normal weight by 7 years of age among those who had higher birth weights. However, these authors studied birth weight and not growth during infancy. In addition, they used, as a measure of relative weight, the weight divided by the height. This index has been shown to be unsatisfactory as a measure of adiposity and the use of some power value of height is indicated[14,15].

In a more recent study, Mellbin and Vuille[4] have reported on the role of infant weight gain as a factor in obesity at 7 and at 10 years of age. Infants who had a rapid weight gain were, at 7 years of age, nine times more likely to be obese if boys, and 1.7 times if girls. At 10 years of age, the ratios were 3.3 and 1.6, respectively. The authors concluded that obesity cannot be considered to be a "continuous process which . . . starts in infancy."

Studies of the relationship between infant weight gain and adult obesity are relatively few. While several studies have related childhood weight status to adulthood, no subjects have been followed serially from infancy to adulthood. Recently, Charney et al[16] determined the obesity status of 366 adults who had been born between 1945 and 1955, and who had measures of their length and weight at 6 weeks, and at 3 and 6 months of age. Using relative weight as the criterion, they found that overweight infants were

2.6 times more likely to be overweight adults than lightweight or normal-weight infants. Furthermore, their data reveal that an overweight infant was 2.2 times more likely to be an obese adult.

Our data demonstrate that the risk of obesity in adolescents who at 1 year of age were, at the extreme of the upper end of the distribution of weight for length is greater than the risk in those, who at 1 year of age, were at the lower end of the distribution. Depending on the sex of the person and whether obesity was assessed by triceps skin-fold thickness or by the relative weight, the risk ratio lies between 2.5 and 4.0

However, since our study was designed to compare adolescents who were drawn from the extremes of those of the 1-year of age distribution of relative weights, the contrasts are higher than if we had used the entire distribution. We may obtain an estimate of the prevalence of obesity in urban youth of a similar socioeconomic environment and ethnic makeup, regardless of their relative weight at 1 year of age, from the data of Stunkard et al.[17] Using the triceps skin fold as a criterion, they found an incidence of 25.4% in boys and 21.9% in girls. (These figures are not remarkably different from the averages of the RW1+ and RW1− youth of our sample: 27.5% in boys and 21.8% in girls.). The ratio of the obesity percentage in RW1+ youth of our sample to that found by Stunkard et al, with no consideration of the 1-year weight, is 1.6 in boys and 1.5 in girls. These values are similar to those reported previously from the study of Mellbin and Vuille[4] but slightly less than the values reported, for adults, by Charney et al.[16] The ratios of Charney et al may be slightly greater than ours because they compared the percentage in adults, who as infants had been overweight, to adults, who as infants had been either lightweight or normal weight. We have compared the percentage in adolescents, who at 1 year of age, had been overweight, with adolescents whose weight was not considered at 1 year of age.

The aforementioned ratios are elevated and suggest an increased risk of adolescent obesity associated with a high relative weight at 1 year of age. However, the risk is not as high as might have been predicted from the research of earlier investigators. The etiology of obesity is complex and, while infant growth is one of the substantial factors, it is not the only, and perhaps not the most important one. Many adolescents do not become obese until the years following infancy. Causative factors associated with the childhood years deserve attention since such factors may, in fact, be responsible for the high prevalence of obesity noted among adolescents and adults.

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Mortality and Morbidity Associated With Pressure- and Volume-Limited Infant Ventilators

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• **The effect of pressure-limited (PL) and volume-limited (VL) ventilation on mortality and morbidity in infants with severe hyaline membrane disease (HMD) was examined in a prospective controlled study. Criteria for mechanical ventilation were Pao_2 value of 50 mm Hg or less or a $Paco_2$ value of 70 mm Hg or greater, while the infant was receiving nasal continuous positive airway pressure (CPAP) at oxygen concentrations (FIO_2) of 0.8 or greater and CPAP of 8 cm H_2O or greater; HMD associated with severe perinatal asphyxia requiring mechanical ventilation in the delivery room.**

Consecutive patients were alternately assigned to receive either PL or VL ventilation. Twenty infants were ventilated with PL machines using low peak inspiratory pressures (mean maximum inspiratory pressure of 28 cm H_2O) and prolonged inspiratory times. Twenty other infants were ventilated with VL machines, using essentially unlimited peak inspiratory pressures (mean maximum inspiratory pressure of 62 cm H_2O) and prolonged expiratory times.

There were no significant differences in survival, incidence of pneumothorax or pulmonary interstitial emphysema, or noteworthy bronchopulmonary dysplasia.

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The relative merits and shortcomings of pressure-limited (PL) and volume-limited (VL) ventilation in infants have been, and continue to be, controversial topics. The simplicity of the PL ventilator, its compact size, and its ability to compensate for air leaks within the system are given attributes. The VL ventilator's versatility, variable inspiratory flow rate, and ability to compensate for ongoing changes in lung compliance are known advantages. When used strictly as a constant tidal volume machine, the VL ventilator is essentially pressure-unlimited.

Recent clinical investigations implicating excessive airway pressure as an important factor in the development of bronchopulmonary dysplasia (BPD) have raised serious questions about the advisability of using VL ventilators.[1,2] In an attempt to resolve some of these questions, a controlled ventilator trial was carried out. Neonates with severe hyaline membrane disease (HMD) who required mechanical ventilation were alternately assigned to either PL or VL machines. The following describes the results.

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PATIENTS AND METHODS

Patients

From Jan 1 through July 1, 1976, a total of 40 infants with severe HMD received endotracheal intubation and mechanical ventilation. Consecutive patients were alternately assigned to either PL ventilators or VL ventilators. All were patients in the newborn intensive care unit of St Paul Children's Hospital, referred from hospitals within a 240-km radius of the city. None were born in our hospital.

Hyaline membrane disease was diagnosed by clinical signs of tachypnea, retractions, grunting, cyanosis corrected by oxygen administration, roentgenographic signs on air bronchograms, and diffuse reticulogranular pattern in the pulmonary parenchyma. Criteria for mechanical ventilation were the inability to maintain a Pao_2 of more than 50 mm Hg while being treated with continuous positive airway pressure (CPAP) with inspired oxygen concentrations (FIO_2) of greater than 0.8 and CPAP of 8 cm H_2O or more, or a $Paco_2$ of 70 mm Hg or more; or HMD associated with perinatal asphyxia requiring intubation and mechanical ventilation in the delivery room. Infants requiring mechanical ventilation for periodic apnea of prematurity were not included. All patients were intubated orally with endotracheal tubes (2.5 mm to 3.5 mm in diame-

ter) and were paralyzed with intravenous pancuronium bromide, 0.1 mg/kg. Paralysis was maintained until signs of noteworthy clinical improvement were observed.

Health Care Maintenance

All patients were cared for in incubators in a neutral thermal environment. Heart and respiratory rate, skin temperature, and blood pressure were monitored hourly. Hypotension (blood pressure of less than 30 mm Hg) was treated by infusions of human plasma protein fraction (Plasmanate) or blood. Samples for blood gas measurements were obtained from either umbilical artery catheters or peripheral arterial punctures at least every six hours. Sodium bicarbonate was given for correction of metabolic acidosis. Blood was administered if the hematocrit reading fell below 35% or the cumulative amount of blood withdrawn for diagnostic studies exceeded 10% of the infant's blood volume. Fluids were administered intravenously at a rate of 50 to 60 ml/kg/24 hr during the first day, and the rate was advanced to 70 to 80 ml/kg/24 hr by day 5. The fluids used on days 1 and 2 were 10% dextrose in water. Electrolyte-containing solutions were given on day three. Fluids were administered through umbilical artery catheters positioned at the aortic bifurcation, umbilical vein catheters positioned in the inferior vena cava above the level of the diaphragm, or by peripheral vein. Feedings by nasogastric tube were started six to 12 hours following admission and advanced toward the goal of 120 to 140 calories/kg/24 hr by five to ten days.

PL Ventilator Protocol

A total of 20 infants received PL ventilation, following protocols in the literature.[3-6] These ventilators were pneumatically operated, electronically time-cycled, constant-flow generators. Ventilators were adjusted to provide FIO_2 of 0.95 to 1.0, a maximum inspiratory pressure (Pmax) of 25 cm H_2O, a rate of 30 breaths per minute, a positive end-expiratory pressure (PEEP) of 5 cm H_2O, inspiratory-expiratory ratio (I:E) of 1:1, and an inspiratory flow rate of 7 to 8 liters/min. The maximum inspiratory time limit was set at 5 seconds. If, after a period of stabilization, the $Paco_2$ value was greater than 65 mm Hg, the ventilator rate was increased to a maximum of 40 breaths per min. If, at the initial settings, the Pao_2 value was less than 50 mm Hg or attempts to decrease the FIO_2 to less than 0.8 were unsuccessful, the I:E ratio was increased to 2:1. If oxygenation was still inadequate at an I:E ratio of 2:1, the I:E ratio was increased to 3:1. If hypoxia persisted, despite an I:E ratio of 3:1, Pmax was increased to 28 to 30 cm H_2O and the PEEP increased to a maximum of 8 cm H_2O.

Once improvement was observed, Pmax was reduced in a stepwise fashion to 25 cm H_2O and PEEP lowered to 5 cm H_2O. Then FIO_2 was decreased to less than 0.8 and the I:E ratio gradually decreased to 1:1. Once the FIO_2 was decreased to 0.6 or less and PEEP levels decreased to 5 cm H_2O, the ventilator's maximum inspiratory time was set at 1 second, neuromuscular blockade was discontinued, and the ventilation rate decreased to 0 (CPAP). The CPAP was then decreased in a stepwise fashion to a pressure of 2 to 3 cm H_2O. Most patients were then extubated.

VL Ventilator Protocol

A total of 20 infants received VL ventilation. These fixed tidal volume machines supply and meter inspiratory gas via a motor-driven piston and a series of electronically actuated clutches that control the piston motion. Ventilator system compliance was calculated daily and varied from 0.28 to 0.43 ml/cm H_2O, depending on tubing length. Ventilators were set at FIO_2 of 0.95 to 1.0; effective tidal volumes (machine tidal volume minus volume lost within the ventilator), 7 to 10 ml/kg; respiration rate, 25 breaths per minute, PEEP, 5 cm H_2O; and an inspiratory flow rate that would provide an I:E ratio of 1:3 to 1:4. This I:E ratio range was selected based on the VL ventilator recommendations of Owen-Thomas et al.[7] The ventilator ceiling pressure was set at 100 cm H_2O. If, after a period of stabilization, the $Paco_2$ value was greater than 65 mm Hg, the ventilator rate was increased to a maximum of 40 breaths per minute. If, at these settings, the Pao_2 value remained less than 50 mm Hg, the PEEP was increased in 1 cm H_2O increments to a maximum of 10 cm H_2O. Once signs of recovery appeared, as witnessed by improvement in arterial blood gas values or consistent decreases in Pmax, FIO_2 and PEEP were reduced in a stepwise fashion to an FIO_2 value less than 0.6 and PEEP of 5 cm H_2O.

Once this level was reached, the ventilator ceiling pressure was set 10 cm H_2O above the current Pmax. Neuromuscular blockade was discontinued and the ventilator was adjusted to provide continuous gas flow throughout the respiratory cycle. The ventilator rate was then gradually decreased to 0 CPAP. The CPAP was decreased in a stepwise fashion until pressures of 2 to 3 cm H_2O were reached. Most patients were extubated at this time.

Complications

The diagnosis of BPD was based on the roentgenographic criteria of Northway et al,[8] Northway and Rosan,[9] and Rhodes and colleagues[10]; or autopsy evidence of interstitial fibrosis; or obliterative bronchiolitis and emphysema. This classification identifies four stages of the disease. Only stages III and IV were considered chronic postventilator lung disease. Since only stage IV appears to have long-term clinical importance, it was considered separately.

Noteworthy barotrauma was defined as roentgenographic or autopsy evidence of

Table 1.—Comparison of Two Infant Groups*

	Infants Receiving PLV, Mean ± SEM			Infants Receiving VLV, Mean ± SEM		
	Total	Survivors	Nonsurvivors	Total	Survivors	Nonsurvivors
Weight, g	1,881 ± 108	2,038 ± 108	1,515 ± 196	2,185 ± 133	2,416 ± 138	1,839 ± 214
Gestational age, wk	33.0 ± 0.6	33.9 ± 0.5	30.8 ± 1.2	34.0 ± 0.8	35.6 ± 1.0	31.6 ± 1.0
Apgar score†	5.8 ± 0.5	5.6 ± 0.6	6.3 ± 0.6	5.0 ± 0.6	5.5 ± 0.7	4.1 ± 1.2
Age at admission, hr	5.5 ± 1.6	6.3 ± 2.2	3.8 ± 1.8	6.8 ± 1.9	10.0 ± 2.9	2.1 ± 0.4
Age at intubation, hr	16.5 ± 4.0	18.7 ± 5.2	11.5 ± 5.5	23.6 ± 5.4	34.9 ± 7.0	6.5 ± 3.5
Pmax, cm H_2O	28.2 ± 0.7‡	27.0 ± 0.7	30.8 ± 1.5	62.1 ± 4.8‡	53.9 ± 4.4	74.4 ± 8.7
Max PEEP, cm H_2O	5.5 ± 0.2‡	5.3 ± 0.1	5.8 ± 0.5	8.1 ± 0.4‡	7.8 ± 0.4	8.5 ± 0.6
Max I:E ratio	1.8:1	1.8:1	2.3:1	1:3	1:3	1:3

*PLV indicates pressure-limited ventilation; VLV, volume-limited ventilation; Pmax, maximum inspiratory pressure; Max PEEP, maximum positive end-expiratory pressure; Max I:E maximum inspiratory-expiratory ratio.
†After 1 minute.
‡$P < .001$.

pulmonary interstitial emphysema, pneumomediastinum, pneumothorax, or pneumopericardium. Since pulmonary interstitial emphysema has been recently incriminated as a harbinger of BPD, it was considered separately.[11] Patent ductus arteriosus (PDA) was diagnosed by the presence of a continuous or systolic murmur, and confirmed by aortography. The condition was considered clinically important if patients were ventilator-dependent after 96 hours of mechanical ventilation or showed overt signs of congestive heart failure. Noteworthy PDA was first treated with diuretics, fluid restriction, and digitalis. If patients were still ventilator-dependent after 36 hours of medical management, the ductus was ligated.

Statistical analysis was carried out using a standard statistical package using cross-tabulation tables for categorical data and a two-tailed Student t test for paired data.

RESULTS

Table 1 compares the clinical data of the two patient groups. Although the infants receiving VL ventilation were heavier (2,185 g vs 1,881 g) and more mature (34 weeks vs 33 weeks) than those receiving PL ventilation, the differences were not significant (weight, $P = .083$; gestational age, $P = .331$). There were no significant differences in Apgar score determined at 1 minute ($P = .279$), in age at admission ($P = .612$), nor in age at the time of endotracheal intubation ($P = .302$).

Mean Pmax generated by the two ventilator systems differed significantly (PL, 28 cm H_2O; VL, 62 cm H_2O; $P < .001$) as did mean maximum PEEP (PL, 5.4 cm H_2O; VL, 8.1 cm H_2O; $P < .001$). In both groups, survivors were treated with lower pressures than nonsurvivors. Mean maximum I:E ratios also differed between the two ventilator groups (PL, 1.8:1; VL, 1:3).

Table 2 compares the mortality and the incidence of BPD, pneumothoraxes, pulmonary interstitial emphysema, and clinically noticeable PDA for the two groups. There were no significant differences in overall survival or in the survival of infants weighing more than 1,000 g or more than 1,500 g. The incidence of BPD (stages III or IV) was similar in both groups. The incidence of noticeable PDA was also similar. The two patients with PDA in the VL ventilator group required surgery; the two infants with PDA in the PL ventilator group did not. The incidence of both pneumothorax and pulmonary interstitial emphysema was lower in the group receiving PL ventilation; however, the differences were not significant. In two infants from the VL ventilator group and one from the PL group, pneumopericardium developed. One complication observed and not previously discussed is the effect of prolonged inspiratory time on the development of pulmonary interstitial emphysema. In two infants receiving PL ventilation, mild pulmonary interstitial emphysema developed. As the I:E ratio increased, there was a progressive deterioration of arterial blood gas values and a worsening of the roentgenographic picture of pulmonary interstitial emphysema. When I:E ratios were decreased, allowing more time for the escape of trapped gas, clinical and roentgenographic improvement followed.

Table 2.—Mortality and Morbidity Associated With PLV and VLV*

	Infant Birth Weight, g				Total, No. (%)
	>2,500	2,001-2,500	1,501-2,000	>1,500	
Infants receiving PLV					
Total No.	3	4	8	5	**20 (100)**
No. of survivors	3	3	7	1	14 (70)
No. with pneumothorax	1	3	2	2	8 (40)
No. with PIE	1	3	2	2	8 (40)
No. with PDA	0	0	2	0	2 (10)
No. with BPD					
Total	0	0	3	3	6 (30)
Stage III	0	0	2	3	5 (25)
Stage IV	0	0	1	0	1 (5)
Infants receiving VLV					
Total No.	5	9	4	2	**20 (100)**
No. of survivors	4	6	2	0	12 (60)
No. with penumothorax	2	3	3	1	9 (45)
No. with PIE	1	6	2	0	9 (40)
No. with PDA	0	1	1	0	**2 (10)**
No. with BPD					
Total	1	3	3	0	7 (35)
Stage III	1	3	1	0	5 (25)
Stage IV	0	0	2	0	2 (10)

*PLV indicates pressure-limited ventilation; VLV, volume-limited ventilation; PIE, pulmonary interstitial emphysema; PDA, patent ductus arteriosus; BPD, bronchopulmonary dysplasia.

Table 3.—Duration of Therapy in Survivors*

	No. of Infants	Mean ± SEM	Range
Infants receiving PLV			
Duration of ventilation, hr	14	106.7 ± 26.0	19-398
Duration of intubation, hr	14	129.5 ± 24.0	50-402
Exposure to $FIO_2 > 0.6$, hr	...	27.0 ± 5.8	(1-72)
Exposure to $FIO_2 > 0.4$, hr	14	85.4 ± 32.6	19-497
Exposure to Pmax > 30 cm H_2O, hr	14	0	0-0
Exposure to PEEP > 5 cm H_2O, hr	14	4.1 ± 2.7	0-32
Infants receiving VLV			
Duration of ventilation, hr	12	132.8 ± 36.6	38-504
Duration of intubation, hr	12	174.1 ± 38.7	50-504
Exposure to $FIO_2 > 0.6$, hr	...	45.0 ± 12.0	4-132
Exposure to $FIO_2 > 0.4$, hr	...	76.9 ± 14.5	14-156
Exposure to Pmax > 30 cm H_2O, hr	...	77.3 ± 17.8	7-137
Exposure to PEEP > 5 cm H_2O, hr	...	60.7 ± 12.5	4-114

*PLV indicates pressure-limited ventilation; VLV, volume-limited ventilation; FIO_2, inspiratory oxygen concentration; Pmax, maximum inspiratory pressure; PEEP, positive end-expiratory pressure.

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Table 4.—Clinica Data on Nonsurvivors*

Patient	Birth Weight, g	Gestational Age, wk	Apgar Score†	Age on Admission, hr	Age at Intubation, hr	Pmax, cm H_2O	Maximum PEEP, cm H_2O	Maximum I:E Ratio	Pneumothorax	BPD	Pathological Diagnosis
Infants receiving PLV											
1	2,300	35	8	3	6	35	8	3:1	+	—	Died at 28 hr HMD streptococcal sepsis, IVH, DIC, pulmonary hemorrhage
2	1,890	33	7	5	5	35	7	3:1	+	+	Died at 130 hr of HMD, DIC, IVH, BPD, PDA
3	1,391	32	7	12	20	35	5	4:1	+	—	Died at 23 hr HMD, pulmonary hemorrhage, tentorial tear, IVH, adrenal hemorrhage, subcapsular hematoma of liver
4	1,270	30	5	0.5	35	25	5	1:1	+	+	Died at 10 days BPD, IVH
5	1,160	28	7	2	3	25	5	3:1	—	—	Died at 71 hr HMD, pulmonary hemorrhage, IVH
6	1,079	28	4	0.5	0.1	25	5	1.5:1	—	+	Died at 13 days HMD, IVH, *Candida* sepsis, BPD
Infants receiving VLV											
1	2,542	35	6	1	5	100	10	1:3	+‡	—	Died at 17 hr HMD, pulmonary hemorrhage, IVH
2	2,280	33	...	3	0.1	68	8	1:3	—	+	Died at 7 days PDA postligation, HMD, hemorrhagic shock, myocardial infarction
3	2,250	33	8	0.5	8	78	8	1:3	+‡	+	Died at 8 days HMD, pneumopericardium, hemopericardium, pulmonary hemorrhage, BPD
4	2,225	33	7	4	30	100	6	1:3	+	—	Died at 5 days HMD, sepsis, DIC
5	1,647	32	1	1	0.1	100	10	1:1	+	+	Died at 36 days severe BPD, cystic fibrosis of the pancreas, IVH, PDA, postligation
6	1,590	31	1	2	6	46	10	1:3	+	+	Died at 81 hr HMD, streptococcal sepsis, DIC, IVH, BPD
7	1,500	30	1	3	3	65	10	1:3	—	—	Died at 28 hr HMD, pulmonary hemorrhage, DIC, tentorial tear, IVH
8	681	26	5	2	0.1	38	6	1:4	+	—	Died at 40 hr HMD, DIC, IVH

*PLV indicates pressure-limited ventilation; VLV, volume-limited ventilation; Pmax, maximum inspiratory pressure; PEEP, positive end-expiratory pressure; I:E, inspiratory-expiratory ratio; BPD, bronchopulmonary dysplasia, HMD, hyaline membrane disease; IVH, intraventricular hemorrhage; DIC, disseminated intravascular coagulation; PDA, patent ductus arteriosus; plus sign, present; minus sign, absent.

†At one minute.

‡Pneumopericardium.

Table 3 summarizes the data regarding duration of therapy. The VL ventilator group required mechanical ventilation approximately 25 hours longer than those receiving PL ventilation. Consequently, endotracheal tubes remained in place longer. Infants receiving VL ventilation were weaned to a FIO_2 value less than 0.6 more slowly. However, duration of exposure to FIO_2 value less than 0.4 was essentially the same. There were important differences between the two groups in time exposed to a Pmax value of greater than 30 cm H_2O. The mean exposure time in the VL ventilator group was 77 hours, while that for the PL ventilator group was essentially 0.

Table 4 summarizes the clinical data of the nonsurvivors. The incidence of pneumothorax and BPD were essentially the same in both groups.

COMMENT

Most clinical investigations of neonatal mechanical ventilation have involved PL ventilators. These PL ventilators deliver a volume of gas by generating a constant predetermined

pressure. The tidal volume delivered is a product of the time over which the pressure is applied and the mechanical properties of the system into which the pressure is directed (a low-compliance lung accepting less volume per unit pressure than a normal lung).[12] Constant pressure ventilators are able to compensate for moderate air leaks within the ventilator system, but are unable to maintain constant tidal volumes in the face of changing resistances and compliances.

Volume-limited ventilators allow the maintenance of a constant tidal volume via a piston or bellows, and continue to do so in the face of changes in lung compliance or in airway resistance. Although these machines all have safety valves set at ceiling pressures when used as strict constant tidal volume machines, they are essentially pressure-unlimited. These VL ventilators are unable to compensate for air leaks, and arbitrary adjustments in machine tidal volumes must be made to compensate for leaks. Recent clinical studies incriminating excessive airway pressures as critical factors in the development of BPD have raised considerable concern regarding the use of these pressure-unlimited machines. Reynolds and Taghizadeh,[1,2] in a retrospective examination of infants weighing more than 1,000 g receiving PL ventilation, observed that after the introduction of a regimen using low Pmax (less than 35 cm H_2O) and high I:E ratios (greater than 1:1), there was an overall increase in survival and a substantial reduction in the postmortem incidence of BPD. Based on these data, the authors concluded that the mechanical trauma caused by elevated airway pressures was the key factor in the pathogenesis of neonatal BPD. Mannino et al[13] observed a noteworthy reduction in the incidence of pneumothorax following the institution of a somewhat similar PL ventilator protocol.

The results of this prospective trial using the PL ventilator protocol of Reynolds et al[3-6] and an alternate protocol in which Pmax was essentially unlimited failed to confirm these impressions. We did not see any noticeable differences in survival or in the incidences of BPD, pulmonary interstitial emphysema, or pneumothorax. The incidence of clinically severe PDA was also similar.

The relatively high incidence of barotrauma observed in both groups is noteworthy, especially since this occurred while the infants were paralyzed. These observations raise questions regarding the clinical value of paralysis. Does paralysis really protect mechanically ventilated patients from barotrauma, or, by abolishing all voluntary muscular activity, does it allow more pressure to be transmitted to the lung, predisposing patients to barotrauma?

There was a general clinical impression that once the acute stage of worsening lung compliance had passed, infants were more easily weaned from PL ventilation. This is also suggested by our data concerning duration of therapy.

Although we failed to prove any significant advantage of one ventilator system over another, any conclusions drawn from this report must be tentative. Although this study was prospective and controlled, certain variables in the patient population could not be controlled. There was an unequal distribution of very low birth weight infants, placing a disproportionate number of these infants in the PL ventilator group. Had larger numbers of infants in this weight category been studied, some differences might have been observed. Given these limitations, the data presented in this report raises certain questions regarding the role of airway pressures in the genesis of BPD. Elevated peak inspiratory pressures may well play an important role in the development of BPD.

However, this has yet to be shown in any prospective clinical study. Before it can be said that one factor is more important than any other, more thoroughly controlled clinical trials examining several ventilator variables must be undertaken.

John W. Reynolds, MD, reviewed the manuscript; John Connett, PhD, performed the statistical analysis.

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Consumptive Coagulopathy

A Complication of Therapy of Solid Tumors in Childhood

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• The association of consumptive coagulopathy and malignancy is thought to be rare in pediatrics. In one patient with Ewing's sarcoma and in two with rhabdomyosarcoma consumptive coagulopathy developed in the presence of either diffuse metastatic disease or an extensive primary tumor. The coagulopathy was a major clinical problem, developing within five days of the onset of chemotherapy. Resolution coincided with the clinical response of the tumor.

(*Am J Dis Child* 132:870-872, 1978)

Consumptive coagulopathy has frequently been reported in adults as a complication of malignancy.[1-5] In pediatrics, however, this association has been infrequently noted.[6-9] Three children with malignant solid tumors in whom consumptive coagulopathy developed soon after the initiation of chemotherapy are reported in this article. One of these patients had an extensive coagulation evaluation and is described in detail. The significance of these findings in the care of children with malignant neoplasms is discussed.

METHODS

Coagulation studies were performed in three patients with solid tumors in whom the disease was complicated by consumptive coagulopathy. Routine studies included complete blood cell counts and venous platelet counts performed by a semiautomated technique. All the blood samples for coagulation studies were drawn by a double syringe technique, and transferred to tubes on ice with 0.1 M buffered citrate as the anticoagulant (1:9 dilution of anticoagulant-blood). The prothrombin time (PT), activated partial thromboplastin time (PTT), and thrombin time (TT) were performed by standard methods.[10] Fibrinogen concentration was assayed using an optical density method,[11] and fibrin-fibrinogen degradation products (FDP) by a modification of the Mersky tanned RBC agglutination technique. The serums for the assay of FDP were treated with thrombin and aminocaproic acid to prevent in vitro fibrinolysis. Factors II, V, VII, and VIII were determined by one-stage assays.[12]

REPORT OF CASES

CASE 1.—A 14-year-old girl had embryonal rhabdomyosarcoma in the gluteal region. Hemoglobin value, WBC count, platelet count, and peripheral blood smear were normal. Initial treatment consisted of radiation therapy during which metastatic disease developed in the bone marrow. Evaluation at this time disclosed pancytopenia (WBCs, 1,400/cu mm; hemoglobin value, 8.8 gm/dl; platelets, 14,000/cu mm), uric acid level, 11.2 mg/dl (normal, 2.0 to 6.4); lactate dehydrogenase (LDH) level, 4,260 IU (normal, 71 to 207); PT, PTT, and TT, within normal limits. Therapy with dactinomycin (500 μg daily for five days) and vincristine sulfate (2 mg/sq m on days 1 and 5) was begun. On the fifth day of therapy, massive, widespread areas of purpura developed. Evidence for consumptive coagulopathy consisted of abnormal PT (26.0 seconds; control, 12.9 seconds), PTT (132 seconds; control, 35.2 seconds), TT (greater than two minutes; control, 22 seconds), hypofibrinogenemia (40 mg/dl), and considerably elevated FDP (328 μg/ml). The platelet count was 3,000/cu mm. The peripheral smear showed marked microangiopathic changes. Euglobulin clot lysis was normal.

The marked coagulation abnormalities did not improve following the administration of 5 mg of vitamin K given intravenously. The patient received a platelet transfusion calculated to produce an increase of approximately 100,000/cu mm. There was no rise in the platelet count six hours later, suggesting the presence of a destructive, thrombolytic state.

Six days later, clinical improvement and correction of the coagulation abnormalities were noted, coinciding with complete remission of the tumor.

The tumor recurred five months later without repetition of the bleeding manifestations. The patient died nine months after diagnosis.

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Coagulation Studies of Case 3						
		Day of Therapy				
	Normal	1	2	4	5	21
Prothrombin time,* sec	9.2-11.2	9.9/10.6	14.9/9.8	11.3/9.4	11.4/9.6	9.4/9.6
Partial thromboplastin time,* sec	32-51	43.3/38.4	41.5/43.2	40.0/42.0	38.8/41.5	27.2/43.0
Thrombin time,* sec	< one third of control	21.8/21.0	> 60/26.7	27.0/19.9	23.8/20.5	21.5/26.5
Fibrin-fibrinogen degradation products, μg/ml	10	...	320	320	320	10
Fibrinogen, mg/100 ml	160-340	305	45	90	125	330
Factor II, %	50-150	...	78	124	124	...
Factor V, %	50-150	...	66	77	77	...
Factor VII, %	50-150	...	110	166	165	...
Factor VII, %	50-150	...	52	76	83	...
Factor IX, %	50-150	...	87	94	67	...
Platelets/cu mm × 10^3	150-350	290	40	14	70	175
Therapy		Cyclophosphamide + vincristine sulfate (day 1)			Cyclophosphamide + vincristine (day 6)	

*Patient value/control value.

CASE 2.—A 4-month-old boy developed a firm, right flank mass measuring 7 × 9 × 2.5 cm, which proved on biopsy to be an embryonal rhabdomyosarcoma. There was no evidence of metastatic disease at diagnosis. Blood cell counts and peripheral blood smears were normal. The platelet count was 417,000 cu mm. The LDH level was 1,598 IU. Therapy was begun with vincristine sulfate (2 mg/sq m weekly for 12 weeks) and dactinomycin (15 μg/kg/day for five days). Twenty-four hours after the first dose of both drugs, there was marked tumor shrinkage, as well as the development of petechiae. The presence of consumptive coagulopathy was confirmed with an abnormal PT (26.3 seconds; control, 9.3 seconds), PTT (90.4 seconds; control, 41.0 seconds), and TT (32.7 seconds; control, 20.6 seconds), hypofibrinogenemia (115 mg/dl), elevated FDP (40 μg/ml), and marked thrombocytopenia (7,500/cu mm). A hemorrhagic pleural effusion further complicated his course.

Clinical improvement, a rising platelet count, and normalization of the coagulation studies were noted after three weeks, coinciding with remission of his tumor.

Local recurrence at the primary site seven weeks after diagnosis was treated with radiotherapy, with a good response. There was no evidence of a coagulation abnormality during the use of this therapeutic modality.

Metastatic disease was recognized at three months and failed to respond to chemotherapy. There was no recurrence of the bleeding manifestations. The patient died six months after diagnosis.

CASE 3.—A 13-year-old boy had a mass in his right distal femur, verified on biopsy as Ewing's sarcoma. Metastatic evaluation disclosed malignant PAS-positive cells in marrow specimens from both iliac crests. The hemoglobin level was 8.8 gm/dl; WBC count, 13,200/cu mm; platelets, 290,000/cu mm; uric acid level, 10.0 mg/dl; and LDH level, 740 IU. Coagulation studies prior to the initiation of therapy gave normal results (Table).

Therapy was begun with cyclophosphamide (500 mg/sq m) and vincristine sulfate (2 mg). Within less than 24 hours, he developed pain and considerable swelling of the biopsy site adjacent to the right knee. Studies at this time (Table) showed evidence of consumptive coagulopathy, ie, abnormal PT and TT, markedly elevated FDP, hypofibrinogenemia, thrombocytopenia, and a microangiopathic hemolytic anemia. The hemoglobin value decreased rapidly from 8.8 to 6.7 gm/dl, and the patient required 1,400 ml of packed RBCs over the following five days to maintain a hemoglobin level of 8 to 9 gm/dl. The swelling in his knee continued to increase for several days; a needle aspiration was performed, with removal of 200 ml of blood.

His coagulopathy began to resolve clinically by day 9 and results of laboratory studies were normal by day 21. The second dose of chemotherapy on day 6 did not exacerbate the consumptive coagulopathy.

A complete remission was attained with actinomycin D. During this time results of coagulation studies remained normal except for the mild, intermittent elevation of FDP up to 20 μg/ml. His disease recurred three months later and he died eight months after diagnosis.

COMMENT

Three patients with extensive solid tumors developed consumptive coagulopathy soon after the initiation of chemotherapy. The coagulopathy was confirmed by a prolonged PT, TT, elevated levels of FDP, hypofibrinogenemia, thrombocytopenia, and a microangiopathic hemolytic anemia. In two of the three patients, the PTT was also abnormal. There was no clinical or laboratory evidence of infection as a cause of the coagulopathy or of serious hepatic dysfunction to account for any of these abnormalities. Two of the three children had obvious metastatic disease at the time of chemotherapy. The third, without confirmed metastases, had a huge primary tumor mass. All three had extremely high serum LDH levels, and hyperuricemia was present in both patients in whom it was measured. This reflected the large masses of tumor noted clinically. Once remission occurred, the coagulation abnormalities resolved.

The presence of a consumptive coagulopathy in these three patients is well documented. This abnormality could be due to disseminated intravascular coagulation secondary to a release of procoagulant material from the tumor into the circulation. However, the possibility of a localized extravascular coagulation in the region of the tumor producing these systemic abnormalities cannot be eliminated by our data.

The association of consumptive coagulopathy and malignancy has been established in adults, occurring most frequently with acute promyelocytic

leukemia[13] and mucin-producing adenocarcinomas.[14] Consumptive coagulopathy, reported twice in association with rhabdomyosarcoma, has not, to our knowledge, been previously reported with Ewing's sarcoma.

In pediatrics, the association of consumptive coagulopathy and malignancy has been limited to isolated case reports of neuroblastoma,[6,7] Wilm's tumor,[8] and histiocytosis X.[9] Komp[15] was unable to verify consumptive coagulopathy in 40 patients with disseminated solid tumors, concluding that this association was not common in pediatrics. Hathaway and Hays[16] studied 32 untreated children with solid tumors, finding evidence of hypercoagulability (consisting of abnormally short thromboelastrograms, elevated factor VIII, and thrombocytosis) in approximately 50%. The only evidence for consumptive coagulopathy was elevation of FDP in one third of the patients.

The consistent relationship between the onset of chemotherapy and of consumptive coagulopathy in our patients may account for the lack of the disease in Hathaway and Hays' untreated patients. Two thirds of Komp's patients were receiving chemotherapy at the time of the study, but the relationship between the onset of chemotherapy and the coagulation studies is not noted. The coagulation studies on our patients were usually normal after their initial episode of consumptive coagulopathy.

The mechanism of initiation of consumptive coagulopathy in association with the treatment of solid tumors is unclear. Colman et al[17] reviewed the role of tissue injury leading to activation of the extrinsic system of coagulation as a mechanism for the initiation of disseminated intravascular coagulation. The presence of thromboplastic materials in malignant tissues has been confirmed.[17-21] Tissue factor from patients with acute promyelocytic leukemia and disseminated intravascular coagulation will trigger coagulation in normal plasma.[18] Considering the large tumor load in these three patients, it seems reasonable to postulate the release of similar thromboplastic material during the initial cytolytic chemotherapy.

The therapy of consumptive coagulopathy in association with malignancy is poorly defined. The experience with heparin has been variable.[2,4,5,13] Successful treatment of the malignancy will lead to resolution of the coagulopathy, but this is often not possible. The coagulopathy in our patients resolved with therapy of their underlying malignancy. Chemotherapy was continued without interruption in all patients in spite of the coagulation abnormality. Heparin was not used in any patient. The therapy of the consumptive coagulopathy was purely supportive. The question of therapy for this entity when tumor control is not possible remains controversial.

The consumptive coagulopathy observed was not only an interesting laboratory abnormality, but a clinically relevant problem in all three patients. The chronologic relationship between the onset of chemotherapy and consumptive coagulopathy, noted previously in the adult literature,[13,20] needs to be emphasized. Drug-induced thrombocytopenia and clinical bleeding within the first five days after chemotherapy is unusual. When this phenomenon is noted, it should not be ascribed to suppression of hematopoiesis secondary to chemotherapy without a diligent search for the possibility of consumptive coagulopathy.

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Limitations of Emergency Room Evaluations of Sexually Abused Children

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• **A retrospective review was performed on charts of all children who were treated in 1975 in the Strong Memorial Hospital (Rochester, NY) emergency room for alleged sexual abuse, suspicious conditions, or complaints related to the genitourinary system, and on a randomly selected comparison sample of children treated for acute otitis media during the same period. In 44 cases of otitis media, pediatric house officers' charting uniformly evidenced adequate care. However, in ten cases of alleged sexual abuse and 29 cases considered suspicious, the evaluations and care were significantly ($.01 > P < .001$) less adequate. The young pediatric house officer deals with these problems, which are complicated by emotional overtones and psychosocial implications, less effectively than those with more clear-cut, routine diagnoses.**

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Despite an increased awareness that sexual crimes against children are a widespread, serious problem[1-4] (representing 8.8% of all cases of child abuse for 1974 in Connecticut[1] and 23.5% of alleged child abuse in the 1966 California pilot study[5]), recognition and subsequent evaluation of the sexually abused child is often difficult.

Physicians are consistently underrepresented in their roles as reporters of the sexually abused child. Brant and Tisza,[6] Browning and Boatman,[7] and DeFrancis[2] have shown that physicians, including pediatric house officers, infrequently report the child victim. Experience in the Rochester (NY) area is similar. Sexual abuse by a parent or parent surrogate represents 27% of the cases of reported child abuse. Only 18 (13%) of the 138 cases of incest investigated in 1975 and 1976 were reported by hospitals. There were no reports by private physicians; the majority of reports came from the police and family courts (unpublished data, April 1977, Monroe County, New York, Department of Social Services).

Of the many factors that relate to low physician reporting, those making it difficult for the physician to identify the sexually abused child are especially pertinent to persons concerned with pediatric education. As in other forms of child abuse, the sexually mistreated child may come to medical attention in a variety of ways, the least common being an actual complaint of assault. Other presentations include undue parental anxiety focused on the genitourinary system, unexplained genitourinary injury, venereal disease (especially in prepubertal children), pregnancy, and less specific behavioral concerns and symptoms.[6-9]

Sexual abuse often involves parental participation (either covertly via neglect or overtly by the parent committing the offense). Available information about the dynamics of the involved families shows them to be closed, rigid, multiproblem families[1,5,7,10] who frequently use denial as a defense mechanism, contributing to difficulties in identification and leading to underreporting. Thus, the physician must maintain a high index of suspicion. It is my impression that another factor contributing to the lack of recognition by physicians is intimately related to the problem of inadequate psychosocial evaluation of children who are seen for medical care.

The hypothesis for this study was that, based on a chart review, children who came to the emergency room with either (1) complaints of sexual assault/abuse or (2) complaints related to the genitourinary system that might be considered suggestive of sexual abuse would be found to have received less adequate evaluation and care by the house officer than those with a common pediatric complaint—otitis media. This would happen because the young pediatrician would insufficiently explore the history of the event, particularly the psychosocial aspects; he or she would not take an adequate history of the present illness, past history, or social history.

METHOD

Charts were reviewed of all patients less than 17 years old who were seen at the Strong Memorial Hospital pediatric emergency department (the major teaching hospital for the University of Rochester (NY) School of Medicine and Dentistry) from Jan 1 through Dec 31, 1975, with the complaint of (1) rape, incest, sexual abuse, or molestation or (2) a complaint or discharge diagnosis related to the genitourinary system that might be interpreted as potentially suggestive of sexual abuse (unexplained vaginal bleeding, genital trauma, recurrent vaginitis, venereal disease in a prepubertal child, unexplained genital pain, pregnancy in a very young adolescent, or excessive parental concern about the genitourinary system). Thirty-nine charts were identified as meeting these criteria. All charts had been completed by pediatric house officers. The review was performed without prior knowledge of the cases, and all information was taken at face value.

After consultation with a senior clinician known for work in this area, criteria were established[11,12] for optimal evaluation and first-contact treatment of sexually abused children. Charts were reviewed, assessing the presence or absence of information in each of seven categories: history of the present illness, including explicit details and an awareness of and attempts at resolution of any discrepancies in the history; medical history, judging general medical background and determining whether or not the alleged present illness (complaint) had previously existed; a brief social history, containing at least a statement about the child's and family's social status; physical examination, namely a brief, complete examination and an appropriate examination of the genitalia; appropriate use of the laboratory; adequate treatment of the stated diagnosis; and arrangements for provision of follow-up care by direct contact with the primary care facility. The house officer's level of postgraduate pediatric education was also noted.

A similar chart review was conducted on a randomly selected 8% (so that sample sizes were approximately equal) sample of the patients who were diagnosed as having

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Audit Results: Charts Containing Adequate Information in Each Category

Audit Category	No. (%) of Charts: Otitis Media (N = 44)	Alleged Sexual Abuse (N = 10)	Suggestive of Sexual Abuse (N = 29)	P*
Present illness	41 (93)	8 (80)	13 (45)	<.001
Medical history	26 (59)	1 (10)	4 (14)	<.001
Physical examination	39 (87)	7 (70)	23 (79)	NS
Description of tympanic membrane or social history	36 (81)	0 (0)	2 (7)	<.001
Correct antibiotic or laboratory test	34 (77)	3 (30)	23 (79)	<.01
Advice on treatment	18 (41)	4 (40)	25 (86)	<.001
Follow-up	36 (82)	3 (30)	22 (76)	<.005

*χ^2 analysis.

acute otitis media from Jan 1 to Dec 31, 1975, in the same emergency room. Charts were examined for the presence of an accurate record of the present illness, a brief medical history, including questions about drug allergies and previous ear infections, physical examination appropriate for the age of the child, description of the tympanic membrane sufficient for diagnosis (decreased mobility and abnormal landmarks or redness), choice of an antibiotic appropriate for the age, advice about symptomatic treatment of fever, vomiting, diarrhea, or pain, and arrangements for follow-up care. The charts of 44 patients with otitis media were reviewed. Statistical analysis was by χ^2.

RESULTS

Otitis Media Cases

The age range of the 44 otitis media patients was 6 weeks to 15 years; 78% of the patients were less than 5 years of age. Sixty-three percent came to the emergency room with a complaint other than ear pain or parental suspicion of otitis media. Results of the audit are presented in the Table. There was a tendency for the more highly trained physicians to write charts containing fewer deficiencies, although the differences between the scores by level of experience did not reach statistical significance. Lower scores were attained in the medical history category (the house officer usually failed to obtain any information about a previous ear infection and often failed to record information about drug allergy) and on providing advice since the physicians frequently failed to indicate that they had discussed a treatment for fever (or analgesia) or prevention of dehydration in the younger children with vomiting or diarrhea.

Sexual Abuse Cases

Of the 39 patients in whom sexual abuse was suspected, chart review identified ten cases in which the presenting complaint was suspicion of sexual assault, and 29 cases in which the presenting complaint was considered suspicious.

Ten children were evaluated for alleged sexual abuse. Only one, a 15-year-old girl who claimed to have been "raped by two strangers," showed evidence of recent traumatic intercourse. The infrequency of positive physical findings is consistent with other reports.[13] Two adolescent boys claimed homosexual assault, and the remaining (aged 2 to 14 years) were girls who had been brought to the emergency room by the mother who suspected that her daughter had been "raped." Of the seven cases where identity of the assailant was known, five were alleged to be either the natural father or the mother's "boyfriend." Uniformly few charts contained adequate medical or social histories. House officers, however, did document the allegation remarkably well and charted satisfactory physical examinations.

Suspicious cases formed the largest category. There were 29 cases involving children aged 1 to 15 years—12 boys and 17 girls. The presenting complaints ranged from "needs to be examined" to "something in his bottom"; the most frequent problems were unexplained vaginal bleeding and recurrent vulvovaginitis. Chart review showed seven of these cases to be unlikely to involve sexual abuse. As one would expect, these charts contained more complete histories. For example, a 9-year-old girl had a discharge diagnosis of "labial contusion"; her mother described the child as having fallen when riding a new bicycle, striking her genital area. The family was intact, there were no discrepancies in the story, and the description of the lesion seemed consistent with the history. In contrast were two examples of the 22 cases that remained suspicious: (1) a 5-year-old boy with an ecchymotic, swollen right scrotum whose parents were unable to agree on the details of the story, and (2) a 14-year-old girl who was treated for recurrent gonorrheal cervicitis. No social history or family history was recorded in her chart despite the fact that, on a previous visit to the emergency room, it had been learned that her younger siblings also had been treated for gonorrhea and that there were many behavioral and family problems.

In the category "suggestive of sexual abuse," the house officers almost always failed to obtain a social or medical history. Only 45% of the charts contained an adequate history of the present illness. However, the physical examination, utilization of the laboratory, treatment, and follow-up recommendation were almost always appropriate, ie, consistent with the stated discharge diagnosis. There was no statistically significant difference in the adequacy of the records by level of education of the house officer.

Results of the chart audit for patients of each type case were compared; there were significant differences ($.01 > P < .001$) on six of the seven categories. Residents uniformly recorded adequate physical examinations in all three groups, and charted complete histories of the present illnesses equally well for children having otitis media and alleged sexual abuse. However, they did less well when the chief complaint or diagnosis was suspicious. This may be because the history for otitis media and alleged sexual abuse is relatively straightforward, ie, a concrete task. Significantly fewer charts for all sexual cases contained satisfactory medical and social histories. The house officer more frequently failed to appropriately utilize the laboratory and arrange follow-up for the children who were alleged to have been sexual-

ly abused. Although these tasks would seem to be straightforward, they actually require complex judgments and decisions. Residents were found to be better in charting advice for the suspicious cases (86% did not contain deficiencies) than for both other groups, because credit was given if the advice was consistent with the stated diagnosis, even though the diagnosis may have been inaccurate. The advice for otitis media and alleged sexual abuse was considered satisfactory only if the house officer recorded that preventative aspects care were discussed—fever, pain, dehydration, behavioral concerns.

COMMENT

Lack of adequate social data in the charts of children undergoing outpatient medical evaluation has been demonstrated by Russo et al,[11] Zuckerman et al,[14] and Chamberlin.[15] It is most striking in the present series that in cases related to sexual abuse where acquisition of social data and a detailed history provide the foundation for the evaluation of the child, 95% of the charts lacked a social history and 46% had an insufficient history of the present illness. This is analogous to diagnosing otitis media without examining the tympanic membrane.

While the 22 suspicious cases in this study fit many of the criteria considered as high risk for sexual misuse, since only chart data were used there is not way to confirm the suspicion. In one case the chart contained an explicit statement that "sexual misuse seemed unlikely." However, there is no reason to believe that other house officers simply failed to record this suspicion in the chart; they uniformly entered sufficient data in the charts of those patients diagnosed as having otitis media, which allows the conclusion that there was little reason to doubt the correctness of the diagnosis and the adequacy of care. This is in marked contrast to those cases where sexual misuse was confirmed or suspected. Uniformly, the house officers failed to record sufficient data to indicate that they had adequately investigated the complaints; they did not explain the discrepancies in the parents' explanations of the injury or illness, and they apparently did not explore the psychosocial areas to determine if there were other suggestions of abuse or neglect. This indicates less than optimal medical practice. Although the relationship between medical records, medical practice, and medical care is debated,[16] Lyons and Payne[17] argue convincingly that "from studies of different populations, with different levels of analysis, at different times, in separate geographical areas, with different measures, using different research designs . . . good medical recording is related to good medical practice."

Reasons for inadequate evaluation of children who may have been sexually abused remain speculative. The general reluctance of society and medicine to acknowledge that sexual crimes are committed against children[1-3] encourages the young pediatrician to close his or her eyes to the facts. Families of abused children (especially where incest or neglect is involved) have been found to be rigid, closed, defensive, and often present a superficial facade of social acceptability,[2,4,11,18-20] not only making interviewing difficult for the inexperienced house officer but also creating a cognitive dissonance if he or she should consider the possibility of abuse. Weiner and Korsch[21] stress the psychological vulnerability of medical students; this vulnerability appears to apply equally to the pediatric house officer. Without suitable role models,[22] feeling largely naive and helpless, untrained, and without an outlet for feelings that might arise should he or she suspect sexual abuse, the pediatrician house officer understandably does not recognize it.

IMPLICATIONS

If Chamberlin[15] is correct in his assertion that the physician's attitude about the usefulness of social information is the factor most likely responsible for its presence, the responsibility for this lies directly with those who train pediatric house officers. Unless senior clinicians who understand the importance of psychosocial influences on health and patient care are available as role models, unless the house officers are taught appropriate interviewing techniques, and unless those in charge demand that appropriate social and historical data be obtained and recorded, problems such as sexual abuse of children will often remain undetected, and medical evaluation and care of children will likely be suboptimal.

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Guide to Oral Theophylline Therapy for the Treatment of Chronic Asthma

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• **Theophylline, when used appropriately, seems to be the most effective noncorticosteroid prophylactic medication for chronic asthma. Dosage, however, requires consideration of the relationship between serum concentration, efficacy, and toxicity, in addition to the variability in rates of elimination. Therapy is initiated with 16 mg/kg/day or 400 mg/day (whichever is less) in divided doses at appropriate intervals depending on the rate of absorption of the product used. If side effects are absent, the dosage is increased at three-day intervals until the age-related mean dosage necessary to produce a therapeutic level, is reached. Final dosage adjustment is generally based on a single determination of serum concentration; dosage requirements generally then remain constant for six to 12 months depending upon the child's growth rate. Dosage adjustment in this manner optimizes benefit, minimizes risk of toxic effect, and avoids excessive numbers of serum theophylline measurements.**

(*Am J Dis Child* 132:876-880, 1978)

The management of chronic asthma frequently requires the use of continuous medication for the suppression of symptoms. Of the various alternatives, continuous use of corticosteroids is best reserved for those patients with serious morbidity that is not relieved by measures with less risk of long-term toxic reactions. Among the noncorticosteroid medications, the sympathomimetic bronchodilators do not yet have a well-defined role as chronic therapy. Cromolyn sodium and theophylline are therefore the initial drugs of choice, and theophylline is the more effective of these two measures.[1] The optimal use of theophylline, however, requires individualization of the dosage regimen so that the serum concentration is maintained within the therapeutic range of 10 to 20 μg/ml.[2,3]

The purpose of the current presentation is to relate our experience with a method for safely and conveniently determining individual theophylline dosage requirements among ambulatory patients with chronic asthma.

INDICATIONS

Patients with reversible airway obstruction, ie, asthma, who have continuous or frequently recurring symptoms are likely to benefit from daily maintenance therapy with oral theophylline.[1,3,4] Nocturnal symptoms awakening the patient as often as once a week, intolerance of normal exercise, daily asthmatic symptoms of cough or dyspnea, frequent requirements for emergency care, or sympathomimetic inhaler abuse all suggest poor control and the need for chronic medication.[5]

The likelihood of benefit from the prophylactic pharmacotherapy of chronic asthma may be increased if the patient with airways obstruction unresponsive to bronchodilators is initially treated with a short course of high doses of corticosteroids.[6] The subsequent return of bronchodilator responsiveness[7] may thereby decrease the frequency of apparent treatment failure with theophylline. Thus, initial pulmonary function tests performed before and after administration of a potent bronchodilator, such as inhaled isoproterenol or injected epinephrine are of value in identifying those

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patients who require this initial measure at the same time that long-term theophylline therapy is initiated.[6]

PRODUCTS SELECTION
Tablets, Liquid-filled Capsules, Suspensions, and Solutions

Theophylline is readily and completely absorbed from the gastrointestinal (GI) tract when administered in preparations that undergo rapid dissolution.[5,9] Available products with these characteristics include an assortment of solutions, a chewable tablet, uncoated tablets, and liquid-filled capsules (Table 1).

Theophylline in the chewable tablet is microencapsulated, which prevents contact with the taste buds as long as the product is not kept in the mouth longer than one to two minutes. The absorption characteristics of this product are similar to those of standard uncoated tablets and liquid preparations (M Weinberger, L Hendeles, L Bighley, unpublished data, 19).

Sustained-Release Products

Since the bronchodilating effects of theophylline relate directly to the serum concentration,[11-13] some children with rapid theophylline elimination rates and labile asthma have required dosing intervals with uncoated tablets or liquids as short as four hours to maintain optimal effect. This is a result of the differences between the peak and the trough serum concentrations, which are greater than 10 μg/ml among 40% of children during a typical six-hour dosing interval with uncoated theophylline tablets.[14] Sustained-release preparations may allow longer dosing intervals or smaller differences between the peak and the trough serum concentrations.

Three dosage forms that are absorbed slower than uncoated tablets and liquids have sufficiently reliable and complete absorption to justify clinical use[9] (Table 1). At least one of the sustained-release preparations (Gyrocaps) has been administered to very young children who cannot swallow the intact capsule. This has been accomplished by sprinkling the beaded contents of the gelatin capsule on a spoonful of soft food and then following it with a tasty liquid of the patient's choice to discourage chewing. The bead coverings have little taste and are acceptable to most children.

DETERMINATION OF DOSE
Initial Dose

The highest dose that can provide the assurance that the serum concentrations will not exceed 20 μg/ml is the lesser of the 16 mg/kg/day or 400 mg/day[15] regimens (Figure). The medication should be administered in equally divided dosages designed to maintain around-the-clock therapy. Preparations that are rapidly absorbed (solutions, suspensions, plain uncoated tablets, and liquid-filled capsules) would generally require administration at approximately six-hour intervals for optimal therapy. Compromises allowing eight hours between bedtime and morning dosages, thus pushing the daytime doses together to about five-hour intervals, are reasonable so long as breakthroughs in symptoms prior to the next dose do not occur (especially during the longer dosing interval at night). Reliable sustained-release preparations provide more realistic dosing schedules for chronic therapy.

Once the initial dosage is begun at appropriate intervals (approximately every six hours for rapid-dissolution products and approximately every eight hours for reliably absorbed sustained-release preparations), patients are instructed to increase the dosage at three-day intervals so long as the drug is tolerated and there is no nausea, vomiting, diarrhea, or headache. These are unlikely at the initial dosage recommended although minor side effects such as nervousness, irritability, or insomnia may occur in some patients and be unrelated to the serum concentration.[16] Most patients who suffer these minor side effects, however, become tolerant of theophylline over a few days; dosage increases should be deferred until such side effects

Table 1.—Theophylline Products With Adequate Bioavailability and Appropriate Dosage Forms for Pediatric Use*

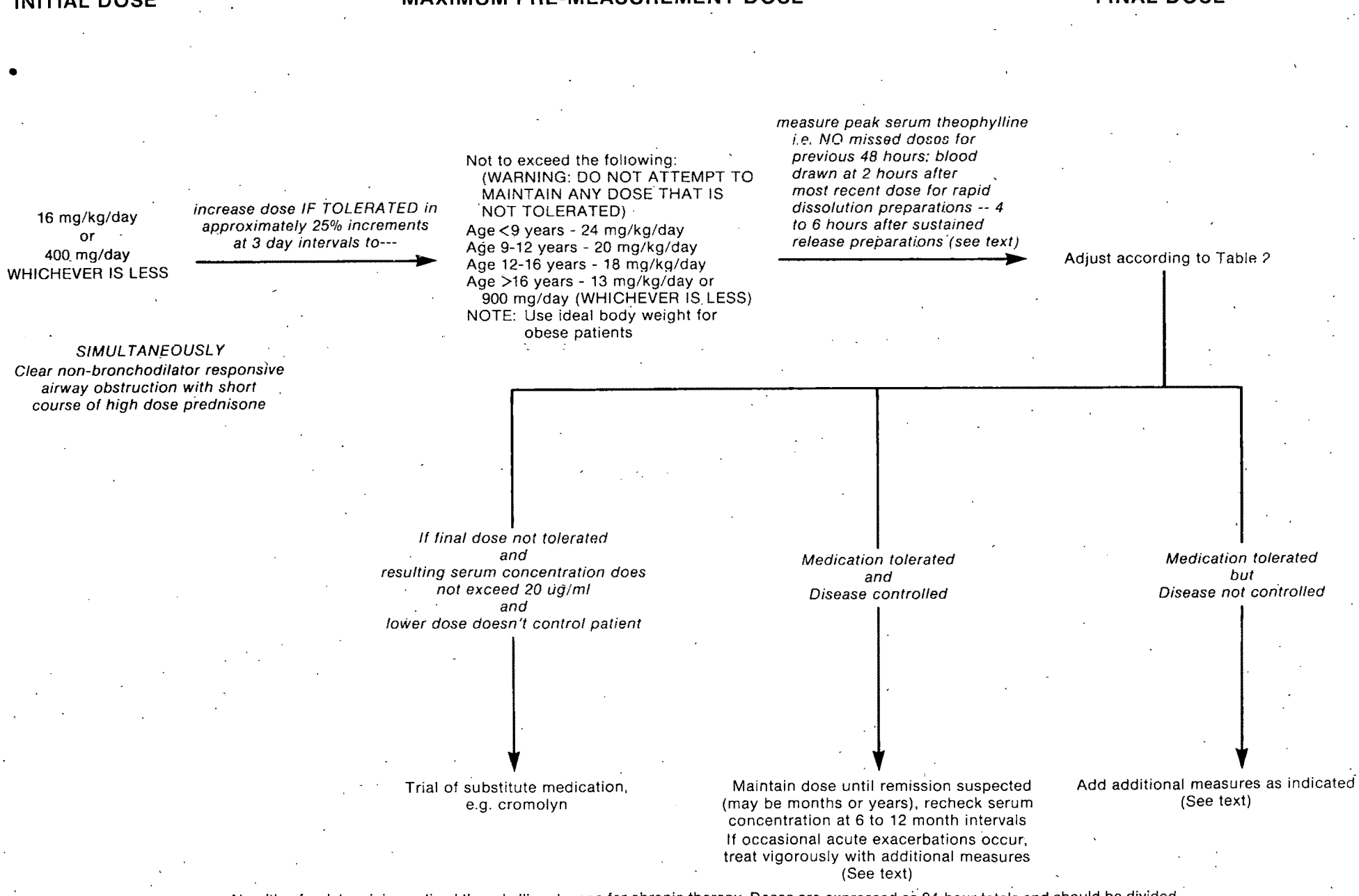
Formulation	Brand Name†	Alcohol Content	Manufacturer	Strength, Theophylline Content	Average Wholesale Cost for 100 mg‡
Tablet	Slo-Phyllin		Dooner	200 mg scored	$0.02
				100 mg scored	.03
	Theophyl-225		Knoll	225 mg scored	.03
	Theolair		Riker	250 mg scored	.04
				125 mg scored	.05
Chewable tablet	Theophyl Chewable		Knoll	100 mg scored	.06
Liquid-filled capsule	Somophyllin		Fisons	250 mg	.04
				200 mg	.04
				100 mg	.05
Oral liquid	Elixicon Suspension		Cooper	20 mg/ml	.10
	Somophyllin Oral Solution		Fisons	18 mg/ml	.09
	Slo-Phyllin-150 Syrup§		Dooner	10 mg/ml	.11
	Theophyl-225	5%	Knoll	7.5 mg/ml	.12
	Quibron Elixir	15%	Mead-Johnson	10 mg/ml	.14
	Elixophyllin Elixir	20%	Cooper	5.3 mg/ml	.15
Sustained release	Slo-Phyllin Gyrocaps		Dooner	250 mg	.03
				125 mg	.06
				60 mg	.09
	Theo-Dur		Key	300 mg scored	.03
				200 mg scored	.04
				100 mg scored	.05
	Theophyl S-R capsules		Knoll	250 mg	.03
				125 mg	.04

*Adapted from Weinberger.[10]

†Caution: Most brand names have more than one preparation in different sizes or concentrations. Prescriptions should include tablet or capsule size or concentration of liquid and route of administration.

‡To nearest cent. Prices based on average wholesale cost to pharmacist as indicated in *1977 Drug Topics Redbook* (Oradell, NJ, Medical Economics Inc).

§Also available as the equivalent Slo-Phyllin GG (the glyceryl guaiacolate included is a harmless inactive ingredient; the concentration is 10 mg/ml).



Algorithm for determining optimal theophylline dosage for chronic therapy. Doses are expressed as 24-hour totals and should be divided to maintain serum theophylline concentrations as stable as possible on an around-the-clock basis. Products with rapid-dissolution characteristics require administration at intervals of approximately six hours for most patients, while sustained-release products may allow eight-hour dosing intervals (some products may allow longer dosing intervals in selected patients).

pass. In about 1% of children[5] and about 4% of adults,[17] these side effects persist, requiring substitution of alternative medication such as cromolyn.

Clinical Titration to Maximum Premeasurement Dose

Dosage increases of approximately 25% should be made at three-day intervals so long as the patient tolerates the medication. If any increase is associated with the adverse effects that relate to serum concentrations greater than 20 μg/ml (eg, nausea, vomiting, diarrhea, or headache), the next dose should be skipped and subsequent doses should be reduced to the highest previously tolerated dosage regimen. The increases in dose at three-day (or greater) intervals should proceed to doses *no higher* than mean age-related requirements (the maximum premeasurement dose in the Figure) prior to measurement of the serum theophylline concentration. These or higher doses should not be continued without measurement of the serum theophylline concentration since 20% of the patients are at a risk of exceeding 20 μg/ml at these doses.[15] Seizures have been observed, generally at serum concentrations greater than 40 μg/ml, and they have occurred without prior warning by the presence of the less-severe manifestations of toxicity.[18]

Table 2.—Final Dose Adjustment Guided by Measurement of Serum Theophylline Concentration

Peak Theophylline Level, μg/ml	Approximate Adjustment in Total Daily Dose	Comment
<5	100% Increase*	If patient is asymptomatic, consider trial off drug; repeat measurement of serum concentration after dose adjustment
5-7.5	50% Increase	
8-10	20% Increase	Even if patient is asymptomatic at this level, an increased serum concentration may prevent symptoms during a viral upper respiratory infection (URI), or heavy exposure to an inhalent allergen or vigorous exertion
11-13	Cautious 10% increase if clinically indicated	If patient is asymptomatic, no increase is necessary; if symptoms occur during URI or exercise, increase as indicated
14-20	None	If "breakthrough" in asthmatic symptoms occur at the end of dosing interval, change to sustained-release product and repeat serum level, measurement
	Occasional intolerance requires a 10% decrease	If side effects occur, decrease total daily dose as indicated
21-25	10% Decrease	Even if side-effects are absent
26-30	25% Decrease	Even if side-effects are absent, omit next dose and decrease total daily dose as indicated; repeat measurement of serum concentration
31-35	33% Decrease	
≥35	50% Decrease	Omit next two doses, decrease as indicated, and repeat measurement of serum concentration

*To avoid potential toxic reaction: (1) assure that the sample represents a peak level obtained at steady state (eg, no missed or extra doses with close approximation of prescribed dosing intervals during previous 48 hours); (2) repeat laboratory determination if not initially performed in duplicate; (3) the increase of 50% or 100% should be made in 25% increments at two-day intervals to further assure safety and tolerance.

FINAL DOSAGE

When the initial clinical titration has resulted in either the highest dose tolerated (if less than the average dose) or the average dose for the patient's age and weight has been attained, a peak serum theophylline concentration should be measured. Since the primary purpose of the serum theophylline measurement is to assure that the highest dose that does not present a risk for a toxic reaction is being used, assurance should be obtained from the history that *no* doses have been missed for at least the previous 48 hours to allow for maximal drug accumulation. Blood should then be drawn at the expected time for the the peak serum concentration to occur as a result of the preceding dose. (A discussion of the various theophylline assay methods, their accuracy, and their practicality for community laboratory facilities is in the April 1978 issue of the *Technical Improvement Service* published by the American Society of Clinical Pathologists.[19]

Peak serum concentrations occur approximately two hours after administration of the plain uncoated tablets and the liquids,[8] and approximately four hours after the sustained-release formulations.[9] Once the peak serum theophylline concentration is obtained and the clinician is assured from the history that the measurement is representative (ie, not artificially altered because of missed doses, extra doses, or atypical dosing intervals), a final dosage adjustment can be made. Recommendations for making the final dosage adjustment based on the serum theophylline measurement (Table 2) are conservative to allow for the possibility that disproportionately large changes in serum concentrations can occur.[20]

Under most circumstances, it is not essential to check the serum theophylline concentration resulting from the final dosage adjustment. Where the dosage change is greater than 25%, however, a repeated serum theophylline measurement is indicated. If the final dosage is tolerated and the disease is adequately controlled, this dosage regimen can then be maintained as long as is necessary with a reexamination of the serum theophylline level at six-month intervals for children during periods of rapid growth, and at 12-month intervals for all others.[15] While theophylline clearance and thus long-term dosage requirements are normally stable over time,[14,15] other drugs and physiological abnormalities may affect the dosage requirements by temporarily altering clearance. Troleandomycin, a macrolide antibiotic, slows theophylline elimination,[21] and the related antibiotic, erythromycin, seems to have similar effects although perhaps to a lesser degree.[22] Heart failure,[23] liver disease,[24] and possibly prolonged fever[14] may have similar effects that result in serum theophylline level increases when chronic dosage is unchanged. Cigarette smoking increases the rate of theophylline elimination,[25] suggesting that patients whose dose is initially determined

while smoking may require a smaller dose when smoking is discontinued to avoid accumulation of drug to potentially toxic serum concentrations.

Transient exacerbations of asthma do not routinely warrant rechecking the serum level. Instead, appropriate additional measures (eg, inhaled or injected sympathomimetics and/or oral or parenteral corticosteroids) may be temporarily needed and if these are not required with excessive frequency they are compatible with an acceptable management plan for the disease.[6]

If the medication is well tolerated but the symptoms are not adequately controlled, additional therapeutic measures should be considered. Cromolyn may result in improvement of the clinical course for some patients when added to appropriate doses of theophylline but most seem not to respond, and no criteria are established for predicting in advance those who will benefit. Oral sympathomimetics seem to be beneficial when additional chronic bronchodilation is indicated by recurring symptoms in the presence of normal post-bronchodilator pulmonary functions. Long-term corticosteroid therapy in the form of alternate-day prednisone or inhaled beclomethasone dipropionate may be required when symptoms and bronchodilator unresponsive airway obstruction repeatedly return after completion of a short course of daily prednisone.

For those patients who cannot tolerate the final dose, reexamination of the serum theophylline concentration is warranted at the highest tolerated dose. If intolerance persists even at peak serum concentrations less than 10 μg/ml (observed in about 1% of children,[5] and more frequently in adults[17]), the drug should probably be abandoned and an alternate chronic medication should be substituted.

COMMENT

The use of theophylline in this manner has been applied to a large ambulatory population of children by the Pediatric Allergy and Pulmonary Division at the University of Iowa. The method has proved practical in that therapeutic levels of theophylline have been achieved in most patients using only one serum measurement and it has been rare for more than two measurements to be required to determine the appropriate final dosage for long-term therapy. Repeated serum measurements at six- to 12-month intervals then seem sufficient for maintaining safe and optimally effective theophylline dosage. In an audit of 200 patients from this clinical service, only two of 172 patients failed to tolerate theophylline and more than 70% experienced full control of their asthma by the explicit audit criteria used.[3]

Nonproprietary Names and Trademarks of Drugs

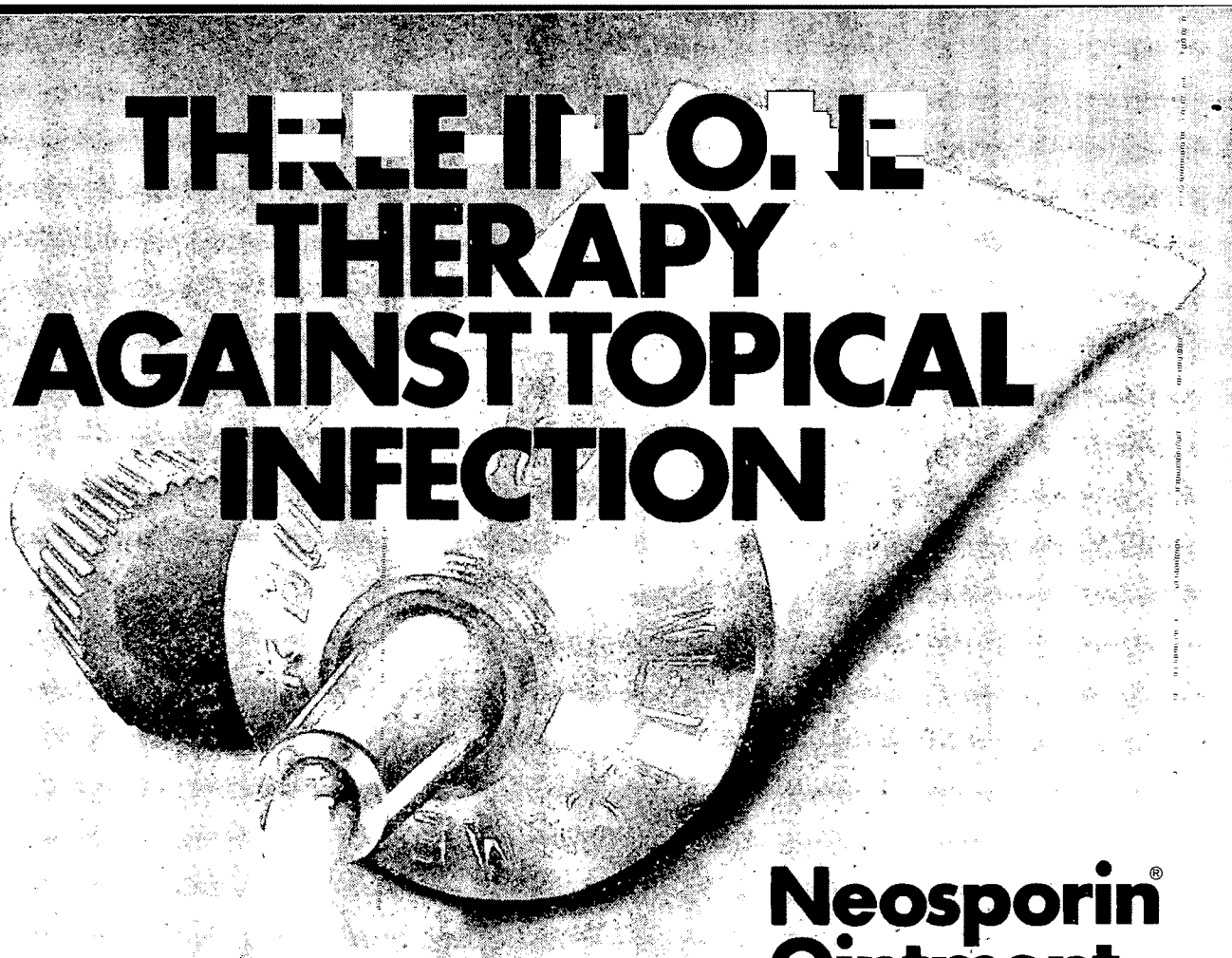
Beclomethasone dipropionate—*Vanceril, Viarex.*

Cromolyn sodium—*Aarane, Intal.*

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WARNING: Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

When using neomycin-containing products to control secondary infection in the chronic dermatoses, it should be borne in mind that the skin is more liable to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

Complete literature available on request from Professional Services Dept. PML.

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Cylert and Cylert Chewable Tablets

(pemoline)

Prescribing Information

Indications: *MINIMAL BRAIN DYSFUNCTION IN CHILDREN*—as adjunctive therapy to other remedial measures (psychological, educational, social).

Special Diagnostic Considerations: The cause of minimal brain dysfunction (MBD) is unknown. Diagnosis of MBD involves the use of medical, psychological, educational, and social tools, since no single diagnostic test is adequate.

MBD is characterized by chronic moderate to severe hyperactivity, short attention span, distractibility, emotional lability, and impulsivity. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present. The diagnosis of MBD must be based upon a complete history and evaluation of the child and not solely on the presence of one or more of these characteristics.

Drug treatment is not indicated for all children with MBD. In the primary therapy of MBD, appropriate educational placement is essential and psychosocial intervention is generally necessary. When these measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or primary psychiatric disorders, including psychosis.

Contraindications: Cylert (pemoline) is contraindicated in patients with known hypersensitivity or idiosyncrasy to the drug. (See ADVERSE REACTIONS.)

Warnings: Cylert is not recommended for children less than 6 years of age since its safety and efficacy in this age group have not been established.

Sufficient data on the safety and the efficacy of the long-term use of Cylert in children with minimal brain dysfunction are not yet available.

A temporary suppression of the predicted growth rate (weight and/or height gain) has been reported for children receiving long-term stimulant therapy. A definite causal relationship between stimulant drugs and this finding has not been established.

Precautions: Liver function tests should be performed periodically during therapy with Cylert. The drug should be discontinued if abnormalities are revealed and confirmed by follow-up tests. (See ADVERSE REACTIONS regarding reports of abnormal liver function tests and jaundice.)

Cylert should be administered with caution to patients with significantly impaired hepatic or renal function.

The interaction of Cylert with other drugs has not been studied in humans. Patients who are receiving Cylert concurrently with other drugs, especially drugs with CNS activity, should be monitored carefully.

Cylert failed to demonstrate a potential for self-administration in primates. However, the pharmacologic similarity of pemoline to other psychostimulants with known dependence liability suggests that psychological and/or physical dependence might also occur with Cylert. There have been isolated reports of transient psychotic symptoms occurring in adults following the long-term misuse of excessive oral doses of pemoline. Cylert should be given with caution to emotionally unstable patients who may increase the dosage on their own initiative.

Usage during Pregnancy and Lactation: The safety of Cylert (pemoline) for use during pregnancy and lactation has not been established.

Fertility, reproduction, and teratology studies were conducted in laboratory animals. Pemoline, in doses of 18.75 or 37.5 mg./kg./day, had no effect on the fertility of male or female rats. The drug, when given to pregnant rats (from gestation day 15 through weaning) and to rabbits (from gestation days 6-18) at these same dosage levels, produced no teratogenic or embryotoxic effects, and had no effect on the viability of the young at birth. However, increased incidences of stillbirths and cannibalization were observed when pemoline was given to rats at these dosage levels, beginning 14 days prior to conception.

Adverse Reactions: Insomnia is the most frequently reported side effect of Cylert; it usually occurs early in therapy, prior to an optimum therapeutic response. In the majority of cases it is transient in nature or responds to a reduction in dosage.

Anorexia with weight loss may occur during the first weeks of therapy. In the majority of cases it is transient in nature; weight gain usually resumes within three to six months.

Stomach ache, skin rashes, increased irritability, mild depression, nausea, dizziness, headache, drowsiness, and hallucinations have been reported.

Elevations of SGOT, SGPT, and serum LDH have occurred in patients taking Cylert, usually after several months of therapy. These effects appear to be reversible upon withdrawal of the drug, and are thought to be manifestations of a delayed hypersensitivity reaction. There have also been a few reports of jaundice occurring in patients taking Cylert; a causal relationship between the drug and this clinical finding has not been established.

There have been reports of dyskinetic movements of the lips, face, and extremities occurring with the use of Cylert. Convulsive seizures have also been reported. A definite causal relationship between Cylert and these reactions has not been established.

Mild adverse reactions appearing early during the course of treatment with Cylert often remit with continuing therapy. If adverse reactions are of a significant or protracted nature, dosage should be reduced or the drug discontinued.

How Supplied: Cylert (pemoline) is supplied as monogrammed, grooved tablets in three dosage strengths:

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37.5 mg. tablets (orange-colored) in bottles of 100 (**NDC** 0074-6057-13)
75 mg. tablets (tan-colored) in bottles of 100 (**NDC** 0074-6073-13)

Cylert Chewable is supplied as monogrammed, grooved tablets in one dosage strength:

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Critical Malnutrition in Breast-Fed Infants

Three Case Reports

Herbert E. Gilmore, MD, Thomas W. Rowland, MD

• Three breast-fed infants of primiparous women had hypothermia, azotemia, and severe dehydration and malnutrition. No disease entities were identified. Although the cause of inadequate breast nutrition was unclear, these cases underscore the necessity for close follow-up and support of first-born breast-feeding babies.

(*Am J Dis Child* 132:885-887, 1978)

Arguments for the biological, psychological, and economic advantages to the breast-fed infant and its mother are well supported.[1-3] Although these benefits have served as an impetus for the general promotion of breast-feeding, it is clear that in certain situations the nursing mother may fail to supply adequate nutrition for her baby.[4]

That such undernourishment may rapidly reach critical proportions is illustrated by a cluster of three breast-fed infants recently admitted to this medical center with profound cachexia, hypothermia, hypoglycemia, and/or shock. It is notable that all were first children of upper-middle-class women. Two sets of parents misinterpreted their infants' infrequent crying and extended sleeping as signaling that breast-feeding was progressing satisfactorily.

From the Department of Pediatrics, Baystate Medical Center, Springfield, Mass.

Reprint requests to Department of Pediatrics, Baystate Medical Center, 759 Chestnut St, Springfield, MA 01107 (Dr Rowland).

REPORT OF CASES

CASE 1.—This patient was transferred to this hospital at age 30 days after he arrived in a local emergency room in profound cardiovascular collapse. He was a 3,340-g infant born to a primiparous woman after a normal full-term pregnancy and delivery.

Physiologic jaundice was the only notable finding in the newborn period. At home, he was breast-fed every four hours, and he initially had a "reasonably good" suck and seemed to be feeding normally. There was no vomiting, diarrhea, or respiratory distress. The mother was taking no medications and was on a normal diet.

One week prior to admission, he began sucking less well and cried more often. He was nursed every three hours, but his appetite seemed to lessen. Because of lethargy and poor feeding, he was taken to a hospital emergency room where he was found to be moribund, hypothermic, and in severe shock. An intravenous line was inserted with some response in the patient's condition, and after a diagnostic lumbar puncture, he was transferred to this hospital.

On examination, he seemed to be a severely marasmic, pale, cold baby with a weak cry. His weight was 2,750 g, 590 g below birth weight. The pulse was 96 beats per minute, with respirations, 44/min. Rectal temperature was 33.1 °C. Blood pressure was not obtainable. Head circumference was 34.5 cm and length was 50 cm (both just below the third percentile for age). Muscle tone was decreased. The remainder of the examination was unremarkable.

The hemoglobin level was 14.4 g/dl, with a hematocrit concentration of 43%. The WBC count was 7,200/cu mm, with 51% polymorphonuclear leukocytes and 41% lymphocytes. Levels of serum sodium were 136 mEq/liter; potassium, 4.9 mEq/liter; chloride, 112 mEq/liter; and CO_2, 14 mEq/liter. The BUN level was 78 mg/dl and the blood glucose level was 178 mg/dl (intravenous dextrose running). Cerebrospinal fluid obtained at the referring hospital showed one WBC and three RBCs per cubic millimeter; glucose level was 10 mg/dl and protein level was 95 mg/dl. Cultures of CSF, blood, urine, stool, and throat failed to show pathogens. Skull and chest roentgenograms were within normal limits, as was an ECG. Repeated lumbar puncture was performed that showed a glucose level of 108 mg/dl. Analysis of arterial blood showed a pH of 7.41, a Po_2 of 118 mm Hg, a Pco_2 of 20 mm Hg, and a bicarbonate level of 12 mEq/liter. The baby received nafcillin sodium and gentamicin sulfate intravenously and was placed in a warmer. After hydration, the BUN decreased to 9 mg/dl.

The baby fed slowly, but gained weight appropriately, and at the time of discharge from the hospital was taking 600 ml of formula (Enfamil) daily without difficulty. At his eight-month evaluation, he seemed like a robust, well-nourished child with a weight of 10 kg (95th percentile), length of 71 cm (75th percentile), and head circumference of 43.8 cm (20th percentile). His developmental achievements and physical examination were normal.

CASE 2.—A 27-day-old male infant, was seen in the emergency ward of this hospital in extremely emaciated and dehydrated condition. He was born to a primiparous 28-year-old woman after a normal pregnancy and delivery; he weighed 2,790 g. Bilateral facial and scalp hematomas were noted at birth, but the immediate postpartum course was uncomplicated. The mother began breast-feeding on the first day, and this was uninterrupted during 24 hours of phototherapy for transient jaundice. Breast engorgement was noted during the first two weeks, but subsequently decreased. A mixture of oxycodone HCl, oxycodone terephthalate, caffeine, aspirin, and phenacetin (Percodan) was used during the first two weeks of breast-feeding for perineal pain (six to eight 4.88-mg tablets per week). Initially the baby fed well on demand every three hours, 15 minutes per breast, but by two weeks did so with less vigor at increasing intervals, occasionally going nine hours without feeding.

At 3 weeks of age, he seemed sleepier and "did not seem to be paying attention at all" during feeding. He "didn't appear to be hungry since he wasn't crying," and the mother believed that his sleepiness meant he was "satisfied." He had no vomiting or diarrhea and was not otherwise ill. When the mother found him "cold to touch," she brought the baby to the emergency ward.

On admission to the hospital, the rectal temperature was 33.0 °C, weight was 2,440 g (350 g below birth weight). Head circumference was 33 cm, the same as at birth and below the third percentile for age. The pulse was 120 beats per minute and thready; systolic blood pressure was 92 mm Hg. Respirations were 28 per minute and shallow, with an occasional Cheyne-Stokes pattern. Blood for glucose determination was not obtained before intravenous dextrose therapy was begun. The WBC count was 17,200/cu mm (55% polymorphonuclear leukocytes, 42% lymphocytes), and hematocrit concentration was 49%. The levels of serum sodium were 134 mEq/liter; potassium, 5.4 mEq/liter; chloride, 110 mEq/liter; bicarbonate, 10 mEq/liter; BUN, 51 mg/dl; creatine, 0.9 mg/dl, and serum acetone, negative. The total serum protein level was 4.9 g/dl. Cerebrospinal fluid analysis was normal, and CSF, blood, urine, and stool cultures were negative. Chest roentgenogram was unremarkable.

Oral feedings were started slowly with progression to full-strength formula (Enfamil) without difficulty. Results of qualitative serum and urine amino acid tests, serum T_3 and T_4, sweat chloride, α_1-antitrypsin, computerized tomography scan of head, and liver function tests were all normal. The stool did not contain excessive amounts of fat, and results of tests for reducing substances were negative.

He was discharged on the 25th hospital day at age 52 days, weighing 2,920 g and has done well on bottle formula (Enfamil). His weight at 2 months of age was 3,430 g (below the third percentile for age), and at 3 months of age, 5,160 g (15th percentile for age). Whole milk feeding was introduced at 4 months of age without problem, and at 8 months, weight was 7,512 g (tenth percentile for age) and height was 66 cm (third percentile for age). He has progressed normally through all diet changes, and presently, at 10½ months of age, is on junior soft table foods. His neurologic development has been normal.

His mother had read pamphlets concerning nursing and had a very positive attitude towards breast-feeding, believing that it "is the best thing for mother and baby." Although she had received very little support from either her mother or her friends, she had had some instruction in breast-feeding in the hospital before and after delivery. In retrospect, she feels that it was not enough to alert her to the signs of breast-feeding failure.

CASE 3.—A 13-day-old infant was referred to this hospital after she was brought to her family pediatrician because of "lack of bowel movements." On examination, she was an extremely emaciated, dehydrated infant with sallow skin color, noticeably diminished skin turgor, and almost complete absence of subcutaneous fat.

Her weight was 1,920 g, a 630-g loss since birth. Head circumference was 32 cm. The temperature was 35.7 °C, pulse, 80 beats per minute, and blood pressure, 80 mm Hg. Other than severe inanition and lethargy, the physical examination was normal. Initial levels of blood glucose were 25 mg/dl; BUN, 35 mg/dl; serum sodium, 148 mEq/liter; potassium, 5.4 mEq/liter; chloride, 116 mEq/liter; and bicarbonate, 6 mEq/liter. The serum bilirubin level was 10.7 mg/dl. Lumbar puncture showed a protein level of 76 mg/dl and a glucose level of 199 mg/dl (intravenous dextrose running). Four RBCs and six lymphocytes per cubic millimeter were seen, and no organisms were evident on Gram's stain. Cultures of CSF, urine, and blood grew no pathogens. The WBC count was 9,400/cu mm with 22% polymorphonuclear leukocytes, 71% lymphocytes, and 7% monocytes. The hematocrit level was 44%. Electrocardiogram was unremarkable. Chest roentgenogram showed "crowding of the markings in the medial portion of the right lower lobe," but was otherwise normal.

The baby received intravenous dextrose and was placed in a warmer. Intravenous nafcillin (20 mg every six hours) and gentamicin (3 mg every eight hours) were administered for 48 hours. By the third hospital day, she was accepting formula feedings well, the serum bilirubin level had decreased to 7.7 mg/dl, and she completed an uneventful five-day stay.

History showed that she was born after an uneventful 36-week gestation, weighing 2,550 g. At delivery, the amniotic fluid was meconium stained and tracheal suctioning was required. Apgar scores were 4 at one minute, and 7 at five minutes, but the chest roentgenogram and blood gas determinations were both normal. The baby did well, and breast-feeding was begun at two days, at which time breast engorgement was evident. On the fourth hospital day, a fever and rash developed in the mother, and breast-feeding was discontinued for 24 hours during which time the mother successfully expressed milk from her breasts. Weight at the time of discharge was 2,380 g (fifth day).

Maternal health was good and no medications were taken during the breast-feeding period. The baby sucked well about 20 minutes from each breast, according to the mother, then slept for three to four hours before awakening. The mother was somewhat concerned that "the breasts did not feel full," but ejection of milk from the nonfeeding breast was noted. The maternal diet was normal, and the mother had augmented her fluid intake. No supplementary formula had been offered, but intermittently 60 to 90 ml of water were given. Other than scarcity of bowel movements, the baby had reportedly seemed well, without vomiting, diarrhea, or fever.

With the support of her husband, the mother, 29 years old, had elected to breast-feed based on her understanding that "it was the best thing for the baby." Instruction was acquired through breast-feeding literature as well as nursing advice after delivery. The pediatrician did not provide specific breast-feeding technique instruction but supported her in her decision to nurse.

After discharge from the hosptial, the baby has done well on formula feedings. Head circumference at age 4 months was

42 cm (50th percentile). At the recent six-month examination, the physical examination was normal, with a weight of 6,600 g and a length of 64 cm.

COMMENT

Breast-feeding failure in primiparous women is a common experience. Of 106 such mothers followed prospectively by Hytten and Yorston,[5] 104 experienced nursing difficulties and 74 discontinued breast-feeding by three months. Forty of these babies showed poor weight gain (less than 141 g per week). Waller[4] estimated that only 30% of primiparous women have a satisfactory breast-feeding experience, 50% have nursing difficulties, and 20% are likely to have outright failure. In 1976, Cole[6] reported an increase in breast-feeding success in 140 mothers (one third stopped by three months), but 42% still encountered difficulties.

Breast-feeding failure has been related to maternal motivation and environmental factors, breast and nipple problems, abnormal babies, and lack of physician and nursing support.[5,7-9] Although the concept of primary inadequacy of lactation has been denied,[10] a number of studies have reported breast-feeding failure for no obvious cause in 40% to 60% of the cases.[4,5]

The three infants in the present report illustrate that, regardless of cause, unrecognized breast-feeding malnutrition may rapidly lead to life-threatening consequences. Although factors, including maternal oxycodone ingestion, breast-feeding jaundice, or unrecognized infection might be suggested as causing feeding failure in our patients, no evidence of metabolic, neurologic, infectious, or other disease states could be detected that would account for the severity of their clinical presentation. In addition, the fact that all were doing well on formula at follow-up evaluation supports a primary role of breast-feeding malnutrition.

Hypoglycemia, hypothermia, hypotension, and azotemia are all well-recognized sequelae to malnutrition and dehydration.[11,12] The effect of such severe calorie-protein deficiency during critical periods of brain growth is problematical,[13] but current data create concern for future psychomotor development in these babies. Fortunately, results of neurologic examination were normal in all three babies on six- to ten-month follow-up.

The undernourished but content breast-fed baby is a well-recognized but uncommon phenomenon.[5,14-16] The mothers of patients 2 and 3 both commented that it was the baby's "good nature" and "satisifed behavior" that had reassured them that nursing was going well. The occurrence of all three cases in primiparous mothers suggests the liability of these women to fail to recognize abnormal breast-feeding behavior in their infants.

Successful breast-feeding requires proper instruction, constant support, and early follow-up. It is hazardous to presume that breast milk's nutritional advantages assure all nursing mothers of providing adequate nourishment to their infants.

Nonproprietary Name and Trademark of Drug

Gentamicin sulfate—*Garamycin.*

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Cushing's Syndrome and Acute Lymphoblastic Leukemia

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• Cushing's disease developed in a 5-year-old girl with acute lymphoblastic leukemia 18 months after her last therapeutic exposure to adrenal glucocorticosteroids. Obesity, hyperpigmentation, striae, osteoporosis, and hirsutism were accompanied by elevated levels of plasma cortisol. These showed no diurnal fluctuation and they were not suppressed by dexamethasone. At autopsy, the adrenal glands were enlarged and the pituitary gland showed increased numbers of basophils of the adrenocorticotropic hormone (ACTH)/melanocyte-stimulating hormone secreting type. Leukemic infiltrates in brain tissue were prominent in the hypothalamus and in the limbic system. It is postulated that the destructive leukemic infiltrate of the limbic system removed a restraining influence on pituitary function, with basophilic hyperplasia, ACTH hypersecretion, adrenocortical hypertrophy, and clinical Cushing's disease the consequences.
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This report describes the development of Cushing's syndrome in a child with acute leukemia. Cushingoid changes associated with the administration of large doses of glucocorticoids[1] are so frequently seen in such patients as to be unremarkable. The present instance is noteworthy in that the clinical and biochemical changes developed when no corticosteroid was being adminstered. Pathological studies showed leukemic infiltrates in the limbic system and the hypothalamus, areas of the CNS known to modulate adrenocortical activity through control of adrenocorticotropic hormone (ACTH) release.[2,3] Changes in the pituitary gland were marked by hyperplasia of basophils, the cell type associated with ACTH secretion.[4] It is postulated that the leukemic infiltrates caused the loss of function of portions of the limbic system important for the restraint of pituitary ACTH release and thereby mediated the patient's hypercortisolism.

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REPORT OF A CASE

A 3-year 4-month-old girl had been well until March 1969 (Fig 1, left). At that time, she fell and was left with a limp. Two months later, anorexia and progressive fatigability developed. When seen in May 1969, she was a pale, slender girl, with a height of 100 cm and a weight of 13.6 kg. Her blood pressure was 104/70 mm Hg. She had extensive generalized adenopathy and hepatosplenomegaly. Results of a neurological examination were normal. Her hematocrit reading was 19% and her WBC count was 7,500/cu mm, with a differential cell count of two polymorphonuclear cells, two eosinophils, 21 lymphocytes, and 75% lymphoblasts. Her platelet count was 32,000/cu mm. Examination of the bone marrow aspirate showed numerous lymphoblasts that confirmed the diagnosis of acute lymphoblastic leukemia.

She was started on a regimen of intravenous vincristine sulfate, 2 mg/sq m weekly, combined with oral prednisone, 60 mg/sq m daily. Allopurinol, 100 mg, was given twice daily for the first five days. After three weeks, vincristine therapy was discontinued and oral methotrexate substituted at a dose of 15 mg weekly. A slight cushingoid appearance developed during the prednisone therapy but it disappeared when prednisone therapy was discontinued after a six-week course. Her leukemia remained in remission while she received methotrexate therapy alone.

Sixteen months after her initial illness she was readmitted to the hospital because of symptoms suggestive of toxic reaction to methotrexate. She had prominent abdominal pain and multiple mouth ulcers. Her physical appearance was that of a thin hyperpigmented girl with a height of 103.5 cm and a weight of 13.5 kg. A bone marrow examination confirmed that her leukemia continued in remission. Treatment was changed to 50 mg of mercaptopurine daily and she was discharged.

Her third admission, three months later was because of weight gain, increased appetite, puffiness of the face, behavioral changes, and headaches. Examination showed a 5½-year-old cushingoid girl (Fig 1, center) with a height of 105 cm and a weight of 21 kg. Her blood pressure was 100/68 mm Hg. She had full, plethoric cheeks, with increased fine black hair on the forehead, in the sideburn area, and on the upper back. The abdomen was protuberant, the liver and spleen were enlarged, skin pigmentation had increased, and there were purple striae of the skin in the flank areas. The fundi were normal bilaterally and no meningeal or focal signs were found. A lumbar puncture showed an opening pressure of 230 mm H_2O and clear fluid containing 464 malignant mononuclear cells per cubic millimeter. Examination of the bone marrow showed no blast forms. Glucosuria was present. The plasma cortisol concentration at 8 PM had increased to 15 μg/dl (normal, less than 7 μg/dl).

The child began receiving intrathecal methotrexate 12 mg/sq m daily for eight dosages. Thereafter, oral methothrexate

herapy was reinstituted. The treatment elieved her of headaches and she remained lmost asymptomatic for the next 11 nonths at which point she suffered a fracure of the left fibula. Roentgenograms howed severe generalized osteoporosis.

Her final hospitalization was at the age of 6 years and 7 months, in June 1972; ospitalization occurred because of comlaints of irritability and headaches. She ad a prominent cushingoid appearance Fig 1, right). Her height was 110 cm and er weight was 27 kg. Hyperpigmentation vas especially noticeable over the joint rominences. The hirsutism and striae had ncreased. She had truncal obesity with a uffalo hump, enlargement of the liver and he spleen, a waddling gait, and generalzed muscle weakness. There was no vidence of virilization. Bilateral edema of he optic disks was present. Both bone narrow and CSF examinations showed eavy lymphoblastic infiltrates.

Endocrine studies during this final admission included a plasma cortisol value ncreased to 53 μg/dl at 8 AM (normal, 10 o 25 μg/dl) and to 56 μg/dl at 8 PM. Dexamethasone, 1 mg, given orally at midnight[5] failed to suppress the plasma ortisol level, the value at 8 AM the following morning being 46 μg/dl (normal, less han 5 μg/dl). Plasma concentrations of uteinizing hormone and follicle-stimulating hormone (FSH) were 1.0 and 4.3 mIU/ml, respectively, both within the normal prepubertal range. The plasma testosterone level was 0.02 μg/dl (normal for age). A fasting blood sample showed a normal growth hormone level of 4 μg/ml with no elevation at two and three hours postprandially. The serum thyroxine level was 6.5 μg/dl, the free thyroxine level was 1.4 μg/dl, and the thyroid-stimulating hormone (TSH) level was 1.4 μU/ml, all within normal limits.

Treatment with vincristine, cytarabine, cyclophosphamide, intrathecal methotrexate, and cranial radiation was unavailing. Grand mal seizures developed and the child's clinical condition deteriorated despite transfusions of platelets and packed RBCs. Death occurred on the third hospital day.

PATHOLOGIC FINDINGS

At autopsy, the general features of Cushing's syndrome were noted. There were numerous cutaneous striae, petechiae, and ecchymoses. A moderate amount of tarry black material was present in the stomach and proximal intestines, without distinct mucosal lesions. Leukemic infiltrates composed of lymphoblasts were found in the kidneys, the liver, and the spleen. The bones showed cortical thinning with enlargement of the medullary cavities. The marrow was packed with lymphoblasts; the number of megakaryocytes was greatly decreased. Mild early pneumonitis was present. The weight of the adrenal glands was at the upper limit of normal for age, with the right gland weighing 4.2 g and the left gland weighing 4.8 g, compared with the normal combined weight of 6.0 ± 1.8 g for girls of 6 to 10 years of age.[6] The cortex was 1 mm thick, well lipidized, and with slight focal nodularity. The thyroid gland, breasts, ovaries, fallopian tubes, uterus, and external genitalia were normal.

No gross abnormality of the pituitary gland was apparent. On histological examination, however, large numbers of medium-sized polygonal cells with abundant small granules were seen; the cytoplasm stained basophilic with hematoxylin-eosin, and magenta with the PAS-orange G stain. These cells were uniformly distributed throughout the anterior pituitary gland (Fig 2) and comprised approximately 25% of the total. They were similar in appearance to basophils of the melanocyte-stimulating hormone (MSH)/ACTH type (A. B. Russfield, MD, PhD, unpublished data, 1972).[7] The cells did not form nodules nor were the changes of Crooke's hyaline degeneration present. The posterior pituitary gland was normal.

The brain weighed 1,200 g, the average for her age being 1,243 g.[8] The leptomeninges were diffusely thickened and discolored yellow, with numerous petechiae and ecchymoses. On section, there was brownish discoloration, softening, and thickening of the entire corpus callosum and septum pellucidum (Fig 3). Similar foci of softening and of discoloration were also present in the region of the anterior commissure, the columns of the fornix, the mammillothalamic tracts, and the globus pallidus. The amygdala and the adjacent uncus were pale bilaterally with the demarcation between gray and white matter obscured. Similar changes were present in the superior part of the hippocampus bilaterally. Microscopically, there was diffuse and dense infiltration of the leptomeninges and the perivascular spaces by lymphoblasts and lymphocytes. Leukemic infiltration was particularly heavy in the corpus callosum, the septum pellucidum, the fornix, the anterior and posterior hypothalamus, the amygdala, the superior hippocampus, and central white matter core of the hippocampal gyrus. Other areas, including the cerebral cortex, were remarkably free of this involvement. Abundant large reactive astrocytes and moderate numbers of macrophages were associated with the parenchymatous infiltrates, suggesting that they were causing necrosis (Fig 4). The leukemic lesions were occasionally associated with focal collections of extravasated RBCs representing microscopic and the larger

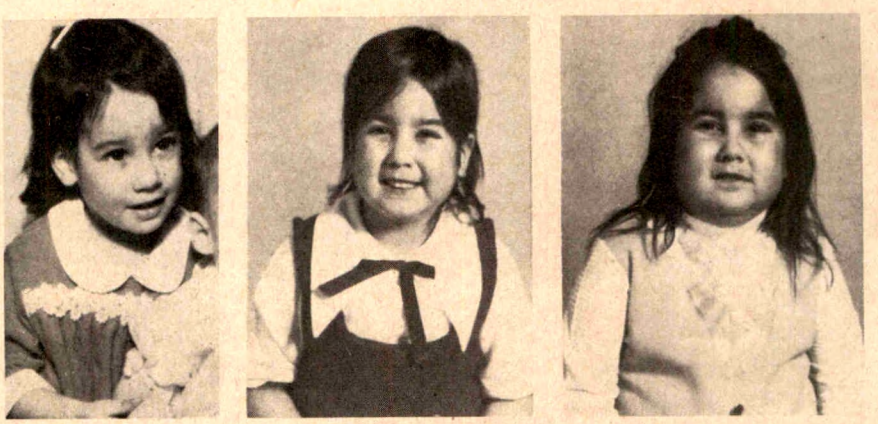


Fig 1.—Progression of Cushing's syndrome. Left, Normal appearance of 3-year 4-month-old girl at time of diagnosis of acute leukemia. Center, Seventeen months after steroid withdrawal at 5½ years of age. Note puffiness of face. Right, Thirteen months later at 6 years and 7 months with noticeable cushingoid appearance, gross disfigurement, and skin hyperpigmentation.

ones, grossly visible petechiae. The nuclei of the hypothalamus were difficult to identify because of the leukemic infiltrates (Fig 5). Their locations could be recognized by the finding of occasional aggregates of nerve cells among the infiltrating cells.

COMMENT

Spontaneously occurring Cushing's syndrome is a rare disease in children.[9,10] Its iatrogenic counterpart is a regrettably frequent complication of long-term administration of adrenocortical steroids for leukemia, nephrosis, and a variety of other disorders.[1,11] This frequency and the fact that the clinical characteristics of the spontaneous disorder are essentially indistinguishable from those of patients with iatrogenic hypercortisolism led initially to the erroneous assumption that the clinical changes in our patient were related to treatment and, thus, to a delay in recognition of the unusual pathogenesis of her symptoms. Truncal obesity, moon facies, and hypertrichosis reappeared 17 months after the withdrawal of corticosteroid treatment. This indicated that the development of Cushing's syndrome at this time was either a second disorder independent of her leukemia or it was somehow related to the latter disorder through a mechanism other than the usual consequence of corticosteroid treatment. The elevated levels of plasma cortisol, the loss of diurnal variation, and the lack of suppression by dexamethasone confirmed the diagnosis.[12] That the adrenocortical hyperfunction was centrally mediated and involved excessive ACTH secretion was suggested by the

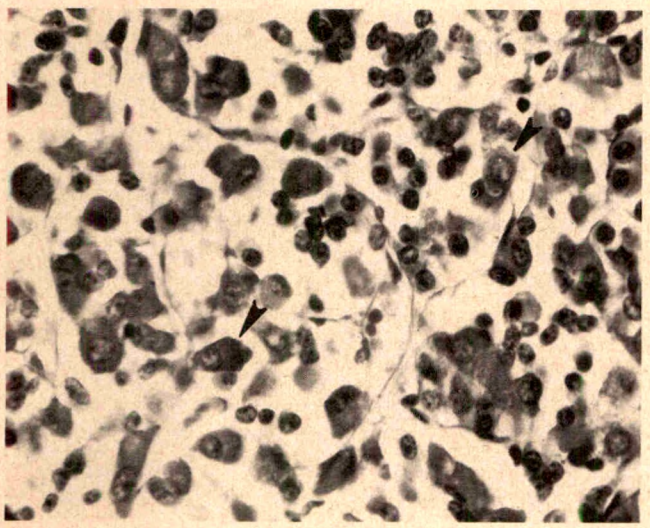


Fig 2.—Abundant medium-sized polygonal and basophilic cells (arrowhead) are interpreted as melanocyte-stimulating hormone/adrenocorticotropic hormone type basophils (hematoxylin-eosin, ×670).

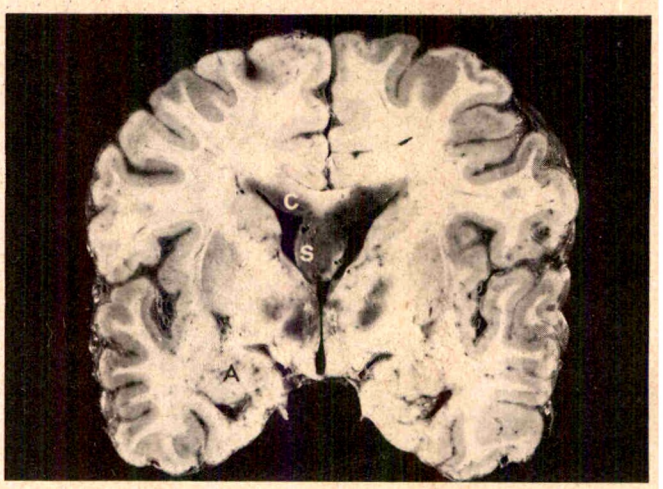


Fig 3.—Coronal section of the brain at level of foramen of Monro showing thickening and discoloration of corpus callosum (C), the normally paper-thin septum pellucidum (S), and similar changes in adjacent structures (see text). A indicates amygdala (×1).

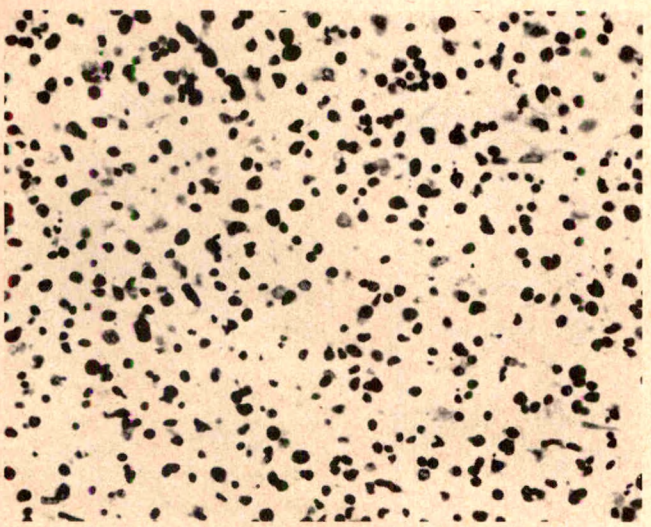


Fig 4.—Infiltrate of hippocampus by lymphoblasts and lymphocytes with associated large reactive astrocytes. Moderate number of large microphages are present, suggesting actual necrosis of brain substance (hematoxylin-eosin, ×400).

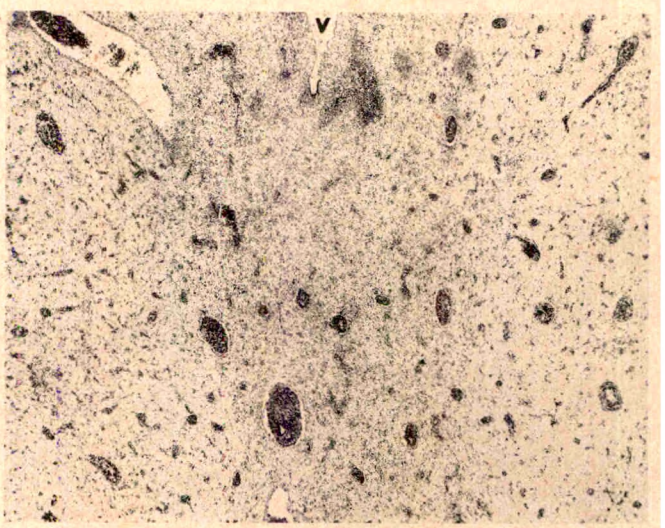


Fig 5.—Posterior hypothalamus inferior to third ventricle (V) with parenchymatous and perivascular leukemic infiltrates (hematoxylin-eosin, ×24).

presence of hyperpigmentation of the skin.[13]

Although the weight of the adrenal glands at postmortem examination was only at the upper limit of normal, hypertrophy is not a requirement for diagnosis of Cushing's syndrome, adrenals of normal size having been found in 10% of the patients with this disorder.[14] The extensive lipidization of the cortices was compatible with hyperactivity secondary to long-term ACTH stimulation. Crooke's cells, the hyalinized basophils associated with autonomous adrenocortical hyperfunction or prolonged corticosteroid therapy,[15] were not present in the pituitary gland. Instead, there was a proliferation of pituitary gland MSH/ACTH basophilic cells of the type seen in other cases of Cushing's syndrome in which it has been argued that the primary change is a disturbance in the hypothalamus that leads to an overproduction of corticotropin-releasing factor (CRF) and increased levels of plasma ACTH.[16]

Information about the central control of adrenocortical function is still incomplete. Studies in man have shown that direct stimulation of the brain can lead to either overproduction or inhibition of adrenal corticoid secretion depending on the particular site of excitation. When certain areas of the limbic system such as the amygdala are electrically stimulated, adrenal steroid secretion is increased. Stimulation of the hippocampus greatly decreases corticosteroid production.[17] Whether those changes in steroid secretion are the result of the modulation of ACTH by a single hormone, CRF, or by a "push-pull" system between CRF (stimulation) and a second substance, corticotropin inhibitory factor (CIF) is still unclear.[18] The sites of production and action of these factors within the CNS and their chemical structures remain to be elucidated. However, in animals, altered ACTH secretion occurs when the hypothalamic areas presumed to contain the neurosecretory cells involved in the production of CRF and CIF are infused with transmitter substances.[18] The level of plasma corticosteroids rises, presumably signifying an increase in ACTH release secondary to CRF stimulation, when cholinergic transmitters are administered,[19] whereas corticosteroid levels drop sharply when noradrenergic transmitters are given.[20] The latter effect can be abolished by pretreatment with alpha blockers.[19,20] These observations suggest that CIF production (or CRF inhibition) depends on norepinephrine-secreting neurons in the brain stem acting on α-receptors.[21]

The strongest evidence pointing to the existence of an inhibitory hormone (CIF) opposite in effect to CRF, produced in and secreted by the CNS, is the fact that adrenocortical hypersecretion occurs in dogs with pituitary glands that have been isolated by extirpation of the brain.[22] In this connection, it is noteworthy that in man proliferation of pituitary gland basophilic cells of the type seen in the present patient has been described after separation of the hypophysis and the hypothalamus by stalk section[23] as well as in association with destructive hypothalamic lesions.[24,25] While Cushing's syndrome has not to our knowledge been noted as a complication of stalk section it has been reported with hypothalamic disease. One such patient had a cerebellar tumor and extensive intracranial hypertension.[26] In another case, Cushing's syndrome was associated with internal hydrocephalus and a dilated third ventricle.[27] These lesions were presumed to have produced stimulation of the hypothalamic areas and secondary ACTH release. However, it may be more logical to assume that loss of brain substance implied loss of function. Thus, the disturbance of endocrine control in these patients with hydrocephalus was more likely due to lesions of the inhibitory centers that freed the target (pituitary) gland from restraint, thereby predisposing it to ACTH hypersecretion.

Leukemic infiltrates of the CNS likewise seldom, if ever, stimulate; they are known to destroy and thus incapacitate the areas involved.[28,29] Sites of leukemic infiltration are most often found in the meninges[30]; occasionally, they involve the brain and the spinal cord[31] but only rarely have they been associated with secondary dysfunction of the endocrine system. Nevertheless, diabetes insipidus has been the initial symptom of acute leukemia in a previously reported case[32] and, in others, hypothalamic invasion of the neurohypophyseal tract has been associated with loss of antidiuretic hormone secretion later in the course of the disease.[33,34] Similarly, the development of hyperphagia and obesity[35] has been associated with leukemic infiltration of the hypothalamus that presumably destroyed the ventromedial nuclei or the ventral noradrenergic bundle.[36] Noteworthy in the context of the present report is the fact that Hyman et al[37] described clinical manifestations of Cushing's disease in children with leukemia of the CNS although no corroborating laboratory data were offered.

The foregoing experimental and clinical information on the modulation of ACTH secretion together with the pathological findings in the brain and pituitary gland of our patient with Cushing's syndrome suggest that the association of the CNS lesions and her endocrinopathy was more than coincidental. The leukemic infiltrates were most prominent in the hypothalamus and in the limbic system, the regions where experimental manipulations most dramatically alter adrenocortical function.[2,3,17] It is our hypothesis that a destructive infiltrate in the limbic system removed a restraining influence on ACTH secretion. Pituitary gland basophilic hyperplasia may have been the result both of absent CIF restraint and unopposed CRF stimulation. Excessive ACTH production with no diurnal modulation ensued, leading to the hyperpigmentation and the hypercortisolism of the child.

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Agnes B. Russfield, MD, assisted in evaluating the histology of the pituitary gland; Edward P. Richardson, Jr, MD, and Gerald Nash, MD, provided reviews of the neuropathology and helped prepare the manuscript.

Nonproprietary Names and Trademarks of Drugs

Allopurinol—*Zyloprim.*
Vincristine sulfate—*Oncovin.*

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CORRECTION

Incorrect Abbreviation.—In the article titled "β-Hemolytic Streptococcus: Its Bacteriologic Culture and Character," published in the May JOURNAL (132:502-508, 1978), the abbreviation CAMP was incorrectly expanded (p 505, column 1, line 51 through 53). It should read the "Christie-Atkins-Munch-Petersen (CAMP) test."

Staphylococcus aureus Colonization and Infection in Newborn Nursery Patients

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• **The correlation between *Staphylococcus aureus* colonization and infection among newborns was studied during a four-year period. Of the 9,423 newborns cultured, 24% were colonized at the time of discharge and in 2% of these an infection developed, whereas only 0.2% of the noncolonized newborns experienced a staphylococcal infection. The weekly colonization rates ranged from 0% to 62%, and outbreaks of infections (two or more concurrent) occurred periodically when the colonization rates ranged from 11% to 57%. Colonization rates per se did not serve as an indicator of an actual or potential outbreak of infection. Instead, the occurrence of two or more concurrent cases of staphylococcal infection or presumptive evidence of an outbreak seems to be a more reliable indicator than colonization monitoring.**

(*Am J Dis Child* 132:893-896, 1978)

The newborn who becomes colonized with *Staphylococcus aureus* after birth is more likely to have a staphylococcal infection develop than one who is uncolonized.[1-7] Because of this, effective control of staphylococcal colonization in the newborn has become an integral component of infection control in the hospital nursery. During the past several years, considerable effort has been devoted to the development of techniques for controlling staphylococcal colonization among newborns.[8-15] One such procedure is that of staphylococcal colonization surveillance. Staphylococcal colonization surveillance was initiated in an effort to recognize any sudden increase in the staphylococcal colonization rate and to permit prompt remedial action before a severe epidemic could develop. The effectiveness of this infection surveillance procedure was studied over a four-year time period by analyzing *S aureus* colonization rates and their influence on the development of nursery-acquired infections among newborns.

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METHODS

Nursery Routines

During the four-year study period, admissions to the nursery averaged 2,300 newborns per year; the average stay was four days. The nursery was situated on the top floor of a 558-bed community-teaching hospital adjacent to the delivery suites and the obstetrical ward. Traffic into the nursery was restricted. The nursery was organized into a cohort system of two small nurseries each admitting 20 consecutive newborns directly from the delivery room. Premature infants or those who were high risk or ill at birth were admitted to the "premie" nursery rather than the general nursery. The newborns remained in their respective cohorts until discharged. Attempts were made to have nursing personnel limit their work to one of the cohort groups during a given shift, but because of the large number of newborns and limited staff, the nurses often worked in both areas.

All nursery personnel followed routine nursery technique. This included a three- to five-minute hand scrubbing with 3% hexachlorophene on entering the nursery and a hand washing with the same preparation before and after each infant contact. Nurses working full-time in the nursery wore scrub dresses and caps or hairnets. Physicians, students, and technicians followed the same hand washing technique and, in addition, wore gowns covering their street clothes.

On admission to the nursery, the newborns were weighed and vital signs were taken. When their temperature was stable, each newborn was bathed with 3% hexachlorophene and, thereafter, given a daily soap bath. During the initial bath, special attention was given to the removal of the vernix and blood, and cleansing of the sulcus around the umbilicus. After the bath, the infant was immediately rinsed with water. No other preparations were applied to the umbilical stump.

Newborns were taken to their mothers for feeding several times a day. Mothers and other family members were instructed to wash their hands before handling the infants.

Culturing Methods

One cotton tip applicator was used to culture both the anterior nares and umbilical stump of all infants at the time of their discharge from the nursery. The swabs were sent to the bacteriology laboratory where they were inoculated onto a sheep's blood agar plate and incubated at 37 °C for 24 to 48 hours. Colonies suggestive of *S aureus* were tested for coagulase by the slide coagulase test.

The nares of personnel assigned to the nursery were cultured for *S aureus* on employment. Personnel with positive cultures were not excluded from the nursery; however, personnel were excluded whenever staphylococcal lesions developed.

Infection Surveillance

Infants were monitored while in the nurseries by the epidemiologist, the attending staff physicians, and the nursing staff for the occurrence of infection. This monitoring continued for 14 days after the infant's discharge from the nursery. Postdischarge information on the occurrence of infection was obtained

Table 1.—Annual *Staphylococcus aureus* Colonization Rates and Infection Rates for Colonized and Noncolonized Newborns

Year	No. of Newborns Cultured	Colonized: No. of Total Newborns Cultured (%)	Colonized: No. of Colonized Newborns Infected (%)	Noncolonized: No. of Total Newborns Cultured (%)	Noncolonized: No. of Noncolonized Newborns Infected (%)
1972	2,335	452 (19.3)	16 (3.54)	1,883 (80.7)	3 (0.16)
1973	2,284	503 (22)	6 (1.19)	1,781 (78)	3 (0.17)
1974	2,386	609 (25.5)	18 (2.95)	1,777 (74.5)	5 (0.28)
1975	2,418	687 (28.4)	13 (1.89)	1,731 (71.6)	7 (0.40)
Total	**9,423**	**2,251** (23.9)	**53** (2.35)	**7,172** (76.1)	**18** (0.25)

through a variety of infection surveillance techniques that included voluntary reporting, telephone surveys, and clinic visits. The attending physician was the most consistent source of such information.

In general, "infection" was defined as the presence of *S aureus* in body tissue or fluid accompanied by a clinical adverse effect (either locally or systemically) on the newborn. "Colonization" was defined as the persistence of *S aureus* on the skin, in body tissues, or in body fluids but without a clinically adverse effect. Therefore, only those newborns with evidence of infection were regarded as such and those without symptoms were regarded as colonized. A detailed discussion of the guidelines used in this study for defining infections can be found in a publication by the Center for Disease Control, Atlanta.[16]

Table 2.—Total Number of Newborns Infected by Place Where Infection Occurred and by Sex

Year	No. of Newborns Infected	Place: In-house Infections (%)	Place: Postdischarge Infections (%)	Sex: M Infected (%)	Sex: F Infected (%)
1972	19	9 (47)	10 (53)	14 (74)	5 (26)
1973	9	2 (22)	7 (78)	6 (67)	3 (33)
1974	23	8 (35)	15 (65)	17 (74)	6 (26)
1975	20	2 (10)	18 (90)	17 (85)	3 (15)
Total	**71**	**21** (30)	**50** (70)	**54** (76)	**17** (24)

RESULTS

Of 9,423 newborns cultured during the study, 2,251 (23.9%) were colonized with *S aureus* before or at the time of their discharge from the nursery (Table 1). *Staphylococcus aureus* infection developed in 53 (2.35%) of the colonized newborns, whereas only 0.25% ($P < .01$) of the noncolonized newborns experienced a staphylococcal infection (Table 1). It should be pointed out that for purposes of analysis, any infant in whom a staphylococcal infection developed prior to the time of routine culture was considered colonized and, therefore, was included in the number colonized. As seen in Table 1, the colonization rate progressively increased during the course of the study, whereas the staphylococcal infection rate among the colonized newborns did not. The unusual decrease in both the number and percent of staphylococcal infections among the colonized newborns in 1973 is unexplained and was not associated with any nursery procedural changes (Table 1). The staphylococcal infection rate among the noncolonized newborns increased with each passing year (Table 1).

Of the 71 staphylococcal infections which occurred in newborns during the study, 70% occurred within 14 days after their discharge from the nursery (Table 2). In addition, it seems from the data summarized that male newborns are particularly prone to colonization and development of staphylococcal infection. During the study, 55% of the colonized newborns were males and 3.15% of these males experienced staphylococcal infections as compared with 1.38% of the 45% colonized females (Table 3). Based on the incidence of infections, 76% of the staphylococcal infections occurred in male newborns during the four-year period (Table 2).

Outbreaks (two or more concurrent cases with a cohort) of staphylococcal infections did occur periodically and an analysis was made to see what correlation, if any, the levels of staphylococcal colonization had on the development of outbreaks of infection. The colonization rates were calculated and summarized on a weekly basis. The prevalence of weekly colonization rates are shown in Table 4 along with the incidence of staphylococcal infections. The weekly colonization rates ranged from 4% to a high of 62%. Outbreaks of infections occurred when the colonization rate ranged from 11% to 57% (Table 4). Other outbreaks occurred when the weekly colonization rates were much greater than the mean values shown in Table 1, but were not associated with reported infections (Table 4).

As an example, for 18 weeks during the study, the weekly colonization rate ranged from 41% to 50% with one or more infections occurring during six (33%) of those 18 weeks, whereas two or more concurrent infections occurred during only three (17%) of the 18 weeks. It is important to note that only 14% of the total number of staphylococcal infections that occurred during the study did so when the weekly colonization rates ranged from 41% to 50% (Table 4).

Because an increased staphylococcal colonization rate is thought to be an indicator of an approaching outbreak of infection, an analysis was made of the daily colonization rates prior to the occurrence of each infection. For the 21 infections that occurred prior to the discharge of the patient, the actual date of onset was used as a reference base; whereas for the 50 postdischarge infections, the date of the infant's discharge from the nur-

Table 3.—Annual *Staphylococcus aureus* Colonization and Infection Rates by Sex

Year	No. of Newborns Colonized	Colonized: No. of Newborns Colonized (%)	Colonized: No. of Colonized M Infected (%)	Noncolonized: No. of Newborns Colonized (%)	Noncolonized: No. of Colonized F Infected (%)
1972	452	265 (58.6)	11 (4.15)	187 (41.4)	5 (2.67)
1973	503	272 (54.1)	3 (1.10)	231 (45.9)	3 (1.30)
1974	609	317 (52)	14 (4.41)	292 (48)	4 (1.37)
1975	687	382 (56.6)	11 (2.88)	305 (44.4)	2 (0.65)
Total	**2,251**	**1,236** (54.9)	**39** (3.15)	**1,015** (45.1)	**14** (1.38)

Table 4.—Correlation Between Weekly *Staphylococcus aureus* Colonization Rates and Occurrence of Infections, 1972-1975*

Colonization Rates, wk	Frequency Distribution of Weekly Colonization Rates, N = 208 (%)	No. of Weeks When 1 or More Infections Occurred (%)	No. of Weeks When 2 or More Infections Occurred (%)	Distribution of Infections, N = 71 (%)
0	1 (0.5)	. . .	. . .	. . .
1-10	30 (14.4)	2 6.7)	. . .	2 (2.8)
11-20	64 (30.8)	13 (20.3)	5 (7.8)	20 (28.2)
21-30	54 (26)	10 (18.5)	3 (5.5)	13 (18.3)
31-40	31 (14.9)	8 (25.8)	6 (19.3)	17 (23.9)
41-50	18 (8.6)	6 (33.3)	3 (16.7)	10 (14.1)
51-60	9 (4.3)	4 (44.4)	3 (33.3)	8 (11.3)
61-70	1 (0.5)	1 (100)	. . .	1 (1.4)

*Percentage data in columns 2 and 3 were calculated by dividing total number of weeks per interval in columns 2 and 3 by total number of weeks per interval in column 1 multiplied by 100.

sery was used as a reference base. That analysis showed that the median colonization rate on the day of onset for the 21 in-house infections and the day of discharge for the 50 postdischarge infections was 34% with a range of 0% to 100%. For the seven days preceeding the infection onset or day of discharge, the daily median colonization rate was 28.3% with the range again being 0% to 100%. When the preceding 14-day and 28-day periods were reviewed, the rates were 28.3% and 27.9%, respectively. Therefore, for the 71 infections, the daily colonization rate did not increase substantially near the day of infection onset.

COMMENT

Newborns rapidly become colonized on body surfaces by microorganisms prevalent in their immediate environment. This is a normal process and ordinarily of little consequence. One such colonizing microbe is *S aureus*. For some still imperfectly understood reasons, staphylococcal infections develop in some newborns who become colonized with *S aureus* within the first few days or weeks after colonization. Therefore, colonization of newborns with *S aureus* is a matter of justifiable concern.

Serious epidemics of staphylococcal infections among newborns[1,2,4,7,17,18] and even their family members have arisen from nurseries.[11,19,20] Therefore, staphylococcal colonization surveillance has become an integral component of the nursery infection control program. The efficacy of using a single swab to culture both the anterior nares and the umbilical stump of each infant at the time of discharge from the nursery as a consistent means of detecting relative changes in colonization rates has been previously documented.[8,21,22]

The 23.9%-colonization rate reported in this study is comparable to colonization rates previously published that ranged from 1.3% to 79%.[1-3,5,8-12,17,20,21,23-25] The difference in the wide range of colonization rates may be attributed to variations in nursery techniques. Although colonization surveillance may have numerous advantages, it is not essential in the prevention of infection.

In this study, weekly colonization rates up to 62% did not necessarily indicate an outbreak situation. These findings suggest that in a nursery, with a high rate of staphylococcal colonization of infants the actual incidence of infection can be low. This finding is contrary to the assumption that the maintenance of low colonization rates of *S aureus* is essential to achieve a low staphylococcal infection rate.[1,6,13,21] In one study, the authors found that skin infections subsequently developed in 20% of the newborns who became colonized, whereas only 1.47% of the noncolonized newborns experienced skin infections.[1] In our study, it seems also that colonization has a causal association with the outcome of a staphylococcal infection, however, our infection rates were much lower for the colonized and noncolonized groups (Table 1).

The periodic variation in the percent of newborns colonized with *S aureus* is unexplained and not associated with nursery routine changes. One investigator reported that colonization rates show seasonal fluctuations.[17] Important differences between highest and lowest seasonal prevalence of *S aureus* occurred nearly every year among newborns with a decline in autumn as a most consistent trend.[17] The data reported in our study

did not conform to noticeable seasonal variations. Large temporary drops in incidence of colonization in our study were probably fortuitous.

Past experience with nursery surveillance has shown that nursery-acquired infections with onset in the nursery represent only a proportion of the total number of infections occurring. The data presented in this study support this conclusion (Table 2). These results are indicative of the importance of postdischarge infection surveillance of nursery patients.

From the data given, it seems that staphylococcal infections are likely to develop in colonized newborns, and male newborns seem particularly prone to colonization and development of an infection (Tables 2 and 3). This data correlates well with an extensive study of the epidemiology of staphylococcal colonization where male newborns were colonized more frequently and experienced more infections than female newborns.[26]

In several previous studies, the investigators succeeded in demonstrating a strong relationship between levels of staphylococcal colonization and infection.[1,2,4,7,9,14] In our study, there was no strong correlation between levels of colonization and infection. Therefore, colonization rates per se did not serve as evidence or an actual or potential indicator of infection outbreaks. Instead, the occurrence of two or more concurrent cases of staphylococcal infection as presumptive evidence of an outbreak seems to be a more reliable indicator than colonization monitoring.

Whether a high colonization rate is bad is determined by whether infection results. This then relates to the question of whether routine staphylococcal colonization surveillance in the nursery ought to be carried out. It is clear from this study and others cited, that a low rate of colonization is somewhat reassuring, but a high rate is not necessarily alarming. Colonization surveillance was instituted to forewarn of possible infections and it is clear from this study that this did not suffice due to many variables, including high colonization rates in nonepidemic or nondisease periods. The value of colonization surveillance is minimal and it is obvious that it is too expensive for adoption everywhere. There is no question that innumerable hospitals maintain exemplary nurseries without recourse to colonization surveillance.

More importantly, we believe that someone should be responsible in every nursery for the supervision of nursery techniques, for determining the frequency of infections, and for deciding when further measures are needed. The prevention of epidemics depends in part on adequate nursery techniques. It was difficult in this study to correlate changes in colonization rates to specific changes in nursery techniques. However, one researcher has stated that a noticeable rise in colonization rate is a warning that some nursery technique is inadequate.[2]

In addition, the detection of an epidemic must depend on private physicians and local clinics to report newborn infections to the hospital infection control personnel. Staphylococci acquired in the nursery often do not produce infection in infants until after discharge from the nursery. As a result, an epidemic may go unrecognized until infection becomes so frequent that cases occurring before discharge increase to a suspicious level. Therefore, nursery infection control programs should include a surveillance system for postdischarge follow-up.

The staff members of the Pediatric Department, Newborn Nursery, and Microbiology Laboratory, St Joseph's Mercy Hospital, Ann Arbor, Mich, provided assistance with this study.

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Gluteal Necrosis With Foot-Drop

Complications Associated With Umbilical Artery Catheterization

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• A newborn infant developed gluteal necrosis and foot-drop associated with umbilical artery catheterization. Clinical course of the infant's illness illustrates that the etiology was multifactorial, being related to the site of catheter tip placement, hypotension, and infusion of hypertonic glucose and other drugs via umbilical catheter.

(*Am J Dis Child* 132:897-899, 1978)

Complications of umbilical artery catheterization have been reviewed extensively.[1,2] The most common vascular complication has been transient blanching of lower limbs with diminished or absent pulses, probably related to arterial spasm. Among other vascular complications are those that are thromboembolic, such as superior mesenteric artery thrombosis, renal artery thrombosis, and necrosis of toes.[3-6] Recently, Rudolph et al[7] reported gangrene of the buttocks following displacement of the umbilical artery catheter tip into the internal iliac artery. Arad and Benady[8] reported similar complication following intra-umbilical infusion of hypertonic dextrose. We are reporting an infant who developed gluteal necrosis and foot-drop under circumstances common to both reports.

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REPORT OF A CASE

A 4.63-kg, 38-weeks'-gestation, large-for-gestational-age infant was born in another hospital; he had Apgar scores of 3 and 8 at one and five minutes, respectively. Because of respiratory distress, the infant was transferred at 8 hours of age to the Intensive Care Nursery at the Medical University Hospital, with an umbilical catheter in place. On admission, the infant had a grand mal seizure that was treated with intramuscularly administered phenobarbital. He was then intubated and placed on the respirator because of bradycardia and gasping respirations. The roentgenogram of the chest and abdomen showed cardiomegaly, and the umbilical artery catheter tip at the level of the L-5 vertebra. Besides continuous L-5 infusion of 10% dextrose, the infant received the following via arterial catheter: (1) 4 mg of furosemide at 12 hours and 5 mg at 26 hours of age because of cardiomegaly and hepatomegaly, (2) 8 ml of 25% dextrose at 24 hours of age because of blood glucose value of 20 mg/dl, (3) 30 ml of 5% human plasma protein fraction (Plasmanate) at 28 hours of age because of blood pressure of 42/24 mm Hg, and (4) 25 mg of phenobarbital at 29 hours of age because of continued seizure activity. By 30 hours of age, an area of cyanosis was noticed in the left gluteal region. The abdominal films showed that the catheter tip was in the left internal iliac artery (Fig 1). The catheter was replaced with the tip at the level of the T-8 vertebra.

The Pao_2 dropped to 33 mm Hg in 100% oxygen at 28 hours of age. Since the serum calcium and hematocrit values were normal, and the electrocardiogram showed right ventricular hypertrophy and right axis deviation, the hypoxemia was considered to be due to persistent fetal circulation. The infant responded to scalp vein infusion of tolazoline (Priscoline) hydrochloride and could be weaned to 25% oxygen over the next two days. Electroencephalogram done at 21 days of age was normal.

The cyanotic area in the left gluteal region had become necrotic by the fifth day of life (Fig 2). Débridement of the necrotic area was performed on the 14th day. A left foot-drop was noticed at this time, accompanied by hypotonia of both the anterior tibial compartment muscles and the gastrocnemius, compatible with sciatic nerve injury. An electromyogram done at 1 month of age was indicative of neuropraxic injury to the sciatic nerve. The necrotic area healed following skin grafting. The muscle function and foot-drop had improved moderately with physical therapy at the time of discharge from the hospital on the 54th day of age.

COMMENT

The optimal level of placement of an umbilical artery catheter, either high, above the diaphragm, or low, at the

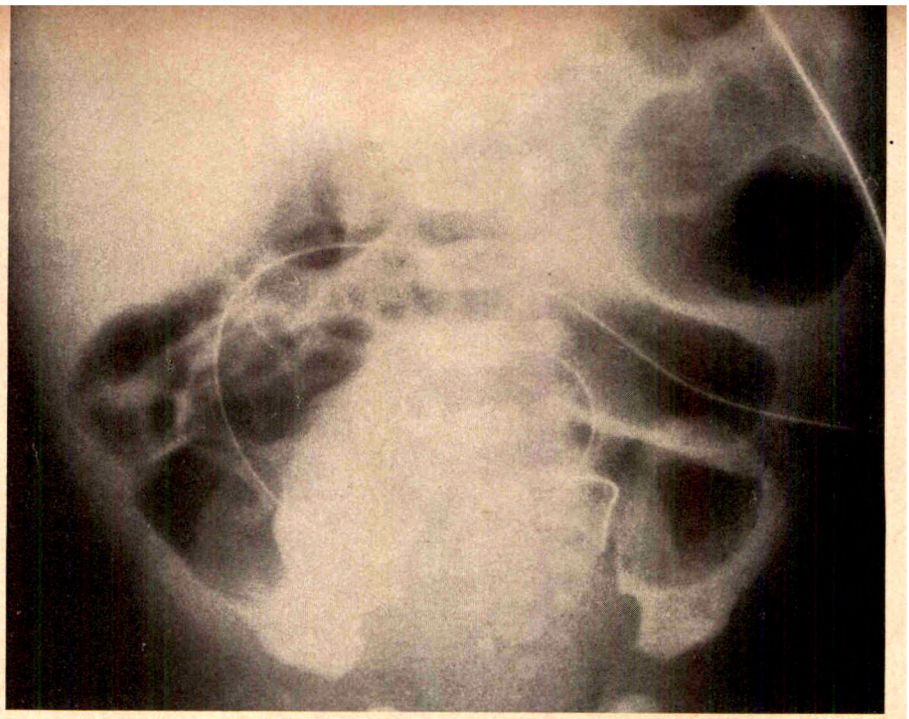


Fig 1.—Roentgenogram of abdomen, showing displaced catheter.



Fig 2.—Necrotic area in left gluteal region.

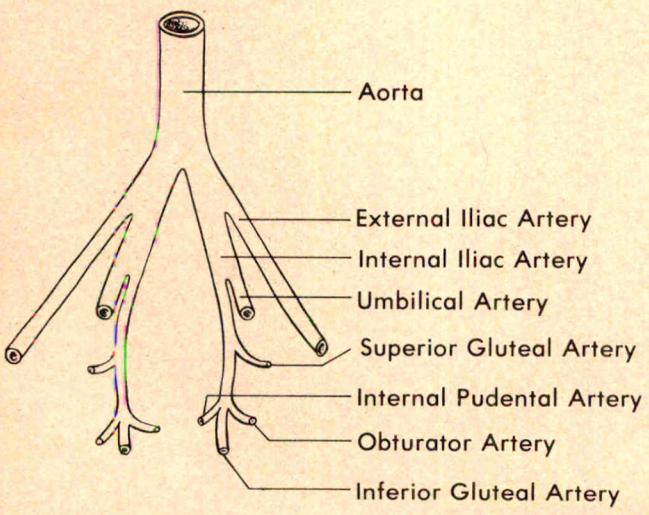


Fig 3.—Major branches of internal iliac artery in fetus and newborn.

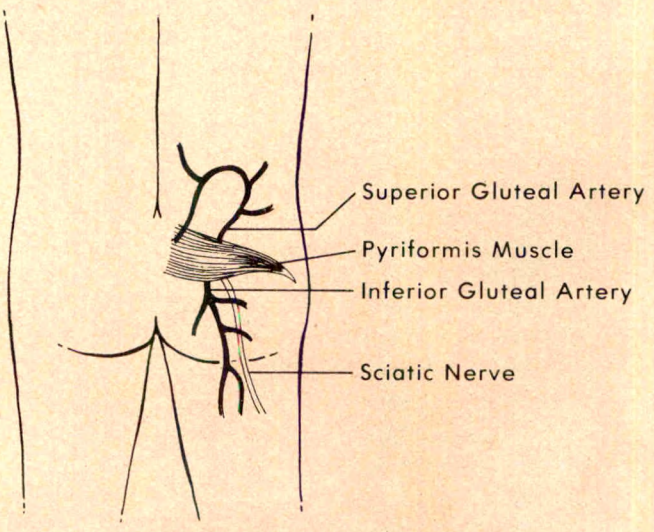


Fig 4.—Arterial blood supply to gluteal region.

level of L-4 or L-5, has been a point of debate. Neal et al[3] demonstrated, by aortography, a high incidence of thrombosis when the arterial catheter tip was above the diaphragm. Since then, the placement of the catheter at L-4 or L-5 has been recommended. No adverse effects of low catheter placement have been published except for a comment by Cochran[9] of increased incidence of blanching of lower extremities with low catheter placement. Rudolph et al[7] reported a case of gangrene of the buttocks following displacement of the umbilical artery catheter tip into the internal iliac artery from its initial site above the diaphragm. However, it would seem that the low-placed catheter would have easier access to the internal iliac artery, as happened in the present case.

The cause of the gluteal necrosis in this case is probably multifactorial. The catheter tip in the internal iliac, at the origin of superior and inferior gluteal arteries, may have caused vascular compromise of the area supplied by these vessels (Fig 3 and 4). Moreover, the hypotension and hypoxemia present prior to the onset of skin necrosis probably resulted in peripheral vasoconstriction, thereby further compromising the vascular supply.[10] The hypertonic dextrose injected for the treatment of hypoglycemia may have initiated intimal damage. A rapid infusion of viscous solution such as 50% dextrose, through end-hole catheters, has been shown to produce a high-pressure jet stream, and thus may add to the vascular insult.[11] Drugs that were injected intra-arterially may have played a role. Loss of limb has been described following inadvertent intra-arterial injection of diazepam.[12] In the prepenicillin era, gluteal necrosis was noticed to occur after accidental intra-arterial injection of bismuth given in the gluteal region for the treatment of syphilis.[13] Similar complications, including foot-drop, have been reported when intramuscular injection of penicillin in the gluteal region was complicated by an accidental intra-arterial injection.[13]

Infants of diabetic mothers have a 15.8% incidence of venous thrombosis as compared to 1% in infants of nondiabetic mothers.[14] Besides renal and adrenal vein thrombosis, peripheral gangrene has also been reported.[15,16] The factors predisposing to venous thrombosis may have similarly played a role in producing arterial thrombosis in our case. Indeed, the gluteal necrosis reported by Arad and Benady[8] occurred in an infant of a diabetic mother. In the present case, even though there was no history of diabetes in the mother, the infant was large for gestational age and had rounded full face similar to that of an infant of a diabetic mother.

Foot-drop has been reported following umbilical arterial injection.[17] The time of onset of foot-drop in our case was uncertain. Since débridement was relatively superficial, it was believed that the sciatic nerve injury occurred at the time of onset of gluteal necrosis. Moreover, since the inferior gluteal artery, also called the sciatic artery, supplies the sciatic nerve, it seems likely that the factors resulting in ischemic gluteal necrosis were also responsible for sciatic nerve damage.

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Hyperuricemia in Congenital Heart Disease

James C. Dearth, MD; Richard B. Tompkins, MD; Emilio R. Giuliani, MD; Robert H. Feldt, MD

• Gout is rarely noted as a clinical problem in secondary polycythemia—even if profound polycythemia exists, as in cyanotic congenital heart disease. A retrospective study of 81 patients with congenital heart disease was done to assess the incidence of hyperuricemia. Twenty of 46 patients with cyanotic congenital heart disease had serum levels of uric acid greater than 8 mg/dl. Thirteen of 16 (81%) cyanotic male patients more than 15 years old had serum levels greater than 8 mg/dl. For cyanotic patients, serum levels of uric acid were related directly to the degree of polycythemia ($r = .44$; $P < .02$). Impaired renal function or drug therapy did not seem to account for the hyperuricemia. Because levels of uric acid greater than 10 mg/dl probably are nephropathic, many of these patients may be incurring subclinical uric acid nephropathy.

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Hyperuricemia is a well-recognized metabolic complication of many myeloproliferative or lymphoproliferative disorders such as lymphoma and leukemia, with the frequency of hyperuricemia being as high as 66% in some of these disorders.[1] Gout occurs in about 5% of these patients. Hyperuricemia in secondary polycythemia, such as that seen in cyanotic congenital heart disease, is not a well-recognized clinical problem, although Somerville[2] described eight patients with gout (one was as young as 16 years old), and other isolated cases have been reported.[3,4] We reviewed the serum uric acid levels in a group of patients who had congenital heart disease in order to determine the incidence of hyperuricemia in these patients and to evaluate the factors that predispose to elevated uric acid levels seen in some patients.

METHODS

Charts were reviewed of all patients undergoing cardiac catheterization during 1974 and 1975 at the Mayo Clinic, Rochester, Minn. Patients who had serum uric acid levels determined served as the study population. Uric acid was measured as part of an automated chemistry group, and the decision to obtain this test was left to the individual clinician (any one of a group of approximately 35). Patients were assigned to two groups: cyanotic if they were cyanotic on examination, had oxygen saturations of less than 90%, or had elevated RBC counts; and acyanotic if they had oxygen saturations greater than 90% or normal RBC counts. Data were recorded concerning diagnosis, age, RBC values, blood pressure, kidney function, drug therapy, and uric acid levels.

Uric acid was correlated with age and RBC count by multiple regression analysis. Mean uric acid values were compared using Student's t test.

RESULTS

Forty-six patients had cyanotic congenital heart disease and represented a wide range of lesions, they included patients who had pulmonary valve atresia with ventricular septal defect, complete transposition of the great vessels, tetralogy of Fallot, complete atrioventricular canal, truncus arteriosus, and ventricular septal defect with severe pulmonary vascular disease.

Thirty-five patients had acyanotic

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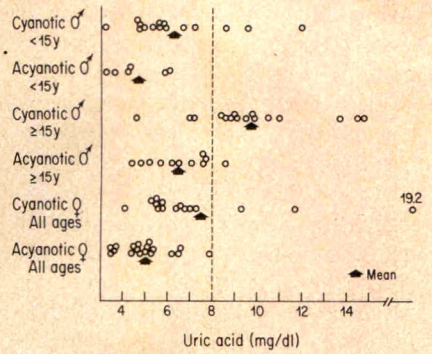


Fig 1.—Serum uric acid levels in patients with congenital heart disease, according to age and sex.

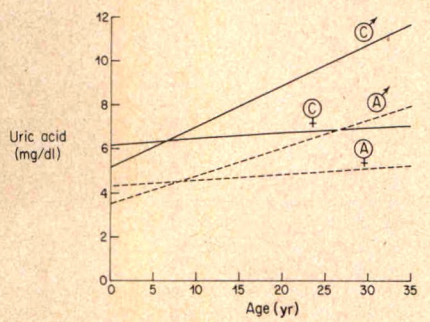
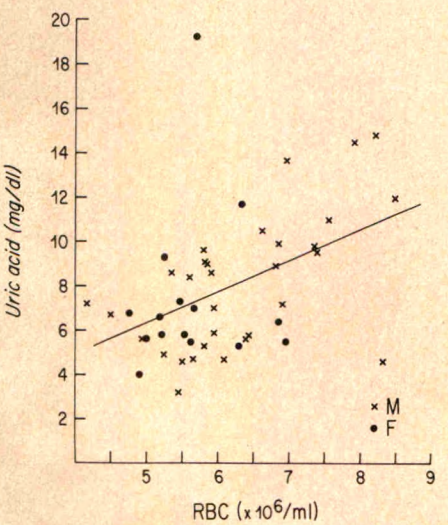


Fig 2.—Serum uric acid levels according to age of patients with congenital heart disease. C indicates cyanotic; A, acyanotic (uric acid = a + b [age]).

Fig 3.—Relationship of serum uric acid levels to erythrocyte count in cyanotic patients with congenital heart disease (uric acid = −0.7243 + 1.4112 [RBC]) (r = .44; $P < .02$).



cardiac lesions; these included patients with atrial septal defect, aortic stenosis, ventricular septal defect, coarctation of the aorta, and partial atrioventricular canal and patients who had had successful repair of cyanotic lesions before this study.

Patients were grouped by age, sex, and presence of cyanosis. Serum uric acid levels for the 16 cyanotic males who were more than 15 years of age were higher (mean, 9.8 mg/dl) than the levels for the acyanotic males more than 15 years of age (mean, 6.5 mg/dl) and for the cyanotic males less than 15 years of age (mean, 6.3 mg/dl) (Fig 1). Within the group of 16 cyanotic males who were more than 15 years old, 13 (81%) had values greater than 8 mg/dl.

Of the 46 cyanotic patients, 21 had values greater than 8 mg/dl; this level is the upper limit of normal for our laboratory. Values were as high as 19.2 mg/dl. Only one of the 35 acyanotic patients had a uric acid level greater than 8 mg/dl.

For male patients, serum uric acid levels were related to age (Fig 2). For cyanotic males, there was a significant (r = .48; $P < .01$) increase in uric acid levels with age. Also, cyanotic males had levels that were statistically higher than the levels of acyanotic males (8.1 vs 5.8 mg/dl, $P < .02$).

For female patients, there was no significant increase in serum acid levels with age (Fig 2). However, cyanotic females had statistically higher levels at all ages than did acyanotic females (7.4 vs 5.0 mg/dl, $P < .02$).

For cyanotic patients, there was a significant (r = .44; $P < .02$) correlation between the uric acid level and the degree of polycythemia (Fig 3). Because uric acid levels increased with age for all male patients (Fig 2), it was important to analyze the relationship of uric acid level to degree of polycythemia, independent of age. The partial correlation coefficient was .38 ($P < .02$). For the acyanotic patients, there was no significant correlation between serum uric acid level and RBC count.

Other potential factors contributing to hyperuricemia were considered. Renal function, as measured by serum creatinine levels, was assessed in all 81 patients. Only two male patients had abnormal creatinine levels (1.3 and 2.1 mg/dl; normal, 0.8 to 1.2 mg/dl), and their uric acid levels were elevated (9.9 and 14.5 mg/dl, respectively). Five female patients had creatinine values between 1.0 and 1.2 mg/dl (normal, 0.6 to 0.9 mg/dl), and in two of these who were cyanotic, the uric acid levels were elevated (11.7 and 19.2 mg/dl).

Hypertension, proteinuria, and the use of thiazide diuretics were also considered as factors and did not appear to influence the uric acid levels. No data were available for our patients on the use of alcohol or aspirin, two other drugs that are believed to influence the metabolism of uric acid. Chart review disclosed no patients with gouty arthritis.

COMMENT

Secondary hyperuricemia is generally considered to be due to either decreased renal excretion of uric acid or increased metabolism of nucleic acid. In our patients, impaired renal excretion is an unlikely factor for the observed hyperuricemia, because severe renal impairment, as reflected by elevated levels of serum creatinine, was not prevalent. Denman et al,[5] however, have shown decreased uric acid clearance in patients with polycythemia vera, including some patients without uremia. In their patients with altered clearance of uric acid, there was no relationship between degree of polycythemia and uric acid levels. The patients in our series had a significant relationship between degree of polycythemia and uric acid level, which indirectly suggests that impaired renal clearance of uric acid did not contribute to the hyperuricemia seen in our patients.

Increased metabolism of nucleic acid is the mechanism for the hyperuricemia seen in lymphoproliferative and myeloproliferative disorders, hemoglobinopathies, pernicious anemia, chronic hemolytic anemias, and secondary polycythemia. Metabolism of purine in polycythemia vera and in the secondary polycythemia of cyanotic congenital heart disease was studied by Yü et al,[3] using ^{15}N-labeled glycine. They demonstrated markedly

increased purine metabolism in both conditions.

The clinical significance of hyperuricemia in cyanotic heart disease is unclear. Our study was a retrospective one, assessing the incidence of hyperuricemia. We do not have follow-up data concerning the eventual development of uric acid nephropathy or arthritis. Nonetheless, the levels of serum uric acid are very high in many patients, being equal to levels seen in the Lesch-Nyhan syndrome[6] and higher than levels seen in many patients with primary gout.

The pathogenesis of gouty arthritis and nephropathy appears to be related to the duration of exposure to hyperuricemia, as primary gout is uncommon before the fourth decade of life.[1] Most patients with cyanotic heart disease either undergo surgical repair or die before that time.

Our concern is that some of our patients may be developing subclinical uric acid nephropathy. Levels of uric acid greater than 10 mg/dl are generally considered to be nephropathic, and these levels were not uncommon in cyanotic males more than 15 years of age. Urolithiasis has been associated with high uric acid levels and is closely correlated with uric acid excretion. Serum uric acid levels of 12 mg/dl or uric acid excretion of greater than 1 g/day is associated with a 50% incidence of urolithiasis.[7] Hyperuricemia can also cause interstitial deposition of uric acid with renal parenchymal damage. Somerville[2] reported no nephropathic changes in the patients in whom renal histologic findings were available.

It seems reasonable to consider a therapeutic trial of allopurinol in selected cyanotic patients with hyperuricemia who are not amenable to surgical repair, because the effectiveness of allopurinol in lowering serum uric acid levels has been demonstrated[8] and the risk of uric acid nephropathy or gouty arthritis is real. In our series, of the two patients who were receiving allopurinol therapy, one maintained a uric acid level of 9.5 mg/dl. The use of allopurinol in hyperuricemic states seems to be safe, although xanthine nephropathy has occurred in an allopurinol-treated patient with lymphosarcoma after xanthine excretion increased more than tenfold,[9] and rarely occurs in patients with Lesch-Nyhan syndrome treated with allopurinol.[10]

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Pyloric Atresia

Carl W. Konvolinka, MD, Robert E. Steward, Jr, MD

• A case of pyloric atresia was treated successfully with side-to-side gastroduodenostomy. The mortality in treated cases is high, due to delay in diagnosis and inadequate relief of the obstruction. Side-to-side gastroduodenostomy or excision of the atresia with pyloroplasty offer the greatest opportunity for a successful outcome, as indicated by a review of the world literature.

(*Am J Dis Child* 132:903-905, 1978)

Pyloric atresia is commonly defined as a lesion that obliterates lumen of the gastrointestinal (GI) tract at the level of the pylorus, and comprises less than 1% of all GI atresias.[1] We saw one of the rarer forms of pyloric atresia, reviewed the literature on the topic, and analyzed the treatment modalities.

REPORT OF A CASE

A 2,380-g male infant was born by elective cesarean section of a mother who had mild preeclampsia but no polyhydramnios. In the child, bile-free, nonprojectile vomiting developed six hours after birth. The vomiting persisted with each attempted feeding. No meconium was passed. He was transferred, aged 50 hours, to our hospital with a diagnosis of intestinal obstruction.

Physical examination showed a well-developed, slightly dehydrated, male infant with no gross abnormalities. The abdomen was flat without evidence of peristaltic waves. The CBC count and serum electrolyte values were normal. Abdominal roentgenogram (Fig 1) showed a dilated stomach and no air below the pylorus. At operation, a 1.75-cm solid tissue mass was found in place of the pylorus, causing complete obstruction of the stomach. The pylorus appeared grossly normal, although the solid nature of it was easily palpable between stomach and duodenum. Incisions in the stomach and duodenum confirmed the presence of the obstructing tissue. The atresia was bypassed, using a side-to-side gastroduodenostomy. The remainder of the GI tract appeared free of atretic segments.

His postoperative course was complicated only by a mild physiologic jaundice. At the age of 1½ years, the child has maintained normal growth and development. There are no symptoms referable to his atresia or its correction.

COMMENT

A mixture of anatomically related lesions are commonly referred to as pyloric atresia. Of the five types of gastric atresia described by Gray and Skandalakis,[2] three are truly pyloric. They are membranous atresia, complete solid atresia, and pyloric discontinuity (Fig 2). The inclusion of a variety of prepyloric anomalies has created some uncertainty as to exactly how many true pyloric atresias have been encountered. Review of the literature also shows variability in the types of surgical repair employed.

Reference to 80 cases of pyloric atresia was found in the world literature.[1-27] Fourteen early cases were autopsy reports. The outcome of four others is unknown. The atresia is classified as membranous in 53 cases; complete, solid atresia in 13; and pyloric discontinuity in ten. Surgical intervention was attempted in 62 infants, with 23 resulting deaths (mortality, 37%).

The differential diagnosis is that of high intestinal obstruction. Since the vomitus is bile-free, the lesion must be located above the ampulla of Vater. Esophageal atresia and pyloric stenosis might be considered, although the former can be eliminated by passing a catheter into the stomach and the latter rarely occurs in infants less than two weeks of age. The correct diagnosis can usually be made in newborn infants who have minimal abdominal distension and nonbilious vomitus by obtaining a roentgeno-

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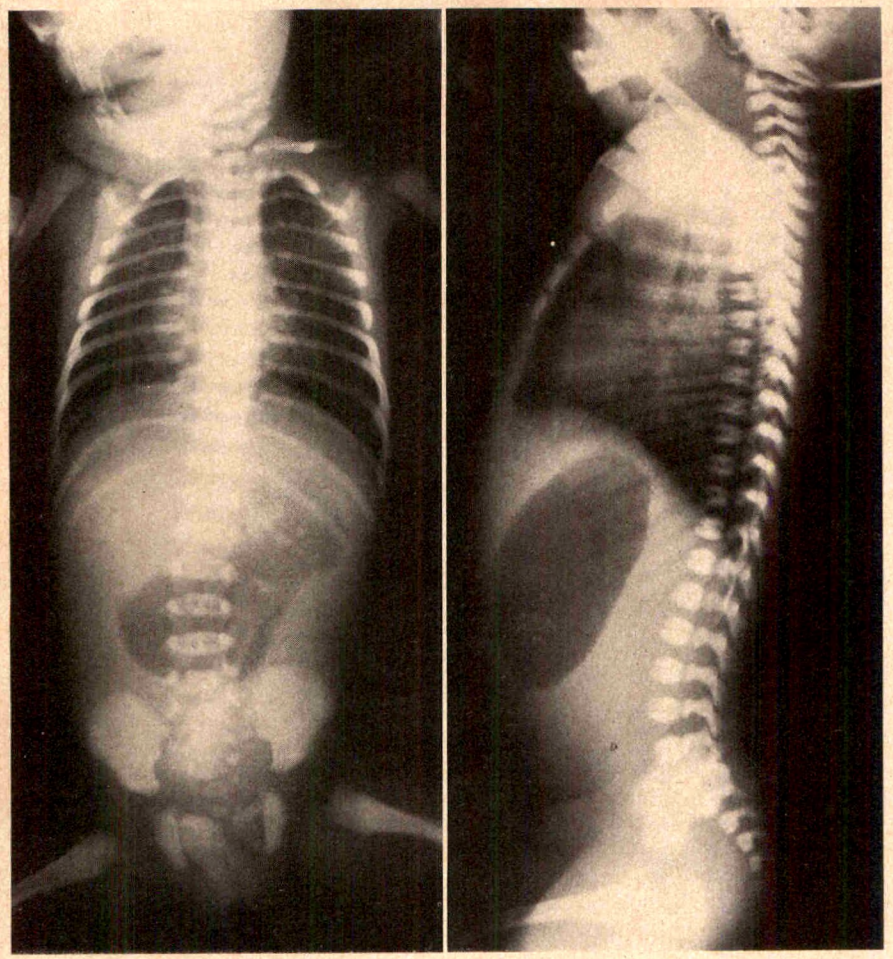


Fig 1.—Left, posteroanterior view, and right, lateral view, of patient with pyloric atresia shows gas-filled stomach. There is complete absence of gas distal to pylorus.



Fig 2.—Three types of pyloric atresia: left, membranous atresia; middle, solid atresia; right, pyloric discontinuity.

gram of the abdomen. The absence of air beyond the pylorus is diagnostic. Polyhydraminios occurs in more than 50% of the mothers of these infants.[20] Prompt diagnosis and treatment minimize the chance of aspiration pneumonitis, metabolic alkalosis resulting from persistent vomiting and, on occasion, gastric perforation. Although it has been suggested that the differential diagnosis is academic, since surgery is always required to relieve an obstruction,[6] failure to appreciate the exact location of the lesion has necessitated reoperation in seven infants who had unrelieved obstruction. Five other infants died from pyloric atresia overlooked at operation.

A variety of surgical procedures have been employed in the management of pyloric atresia. The Table summarizes these procedures and indicates their relative merit. Bennett,[6] in 1937, recommended electrocoagulation to destroy a pyloric membrane. This would seem to have no place in modern management, since stenosis or complete obstruction is likely to occur from subsequent scarring. Neither excision nor perforation of the membrane alone appears to be a reasonable choice, because six of 11 patients so treated required further surgery, and one of these died. Two cases of pyloric atresia were mistakenly treated by a Ramstedt pyloromyotomy. One patient died, and the other survived following reoperation.

Four other methods commonly employed are gastrojejunostomy, excision of the membrane with pyloroplasty, gastroduodenostomy, and resection of the atretic segment with end-to-end or end-to-side anastomosis. Although gastrojejunostomy was the most commonly used procedure, it carried both a noteworthy failure rate (59%) and a high mortality (55%). At

Surgical Treatment of 62 Cases of Pyloric Atresia

Operation	No. (%)		
	Times Employed	Failures*	Mortality
Gastrojejunostomy	22	13 (59)	12 (55)
Excision of membrane and pyloroplasty	16	3 (19)	2 (12.5)
Gastroduodenostomy	11	2 (18)	2 (18)
Excision of membrane only	8	4 (50)	1 (12.5)
Resection of atretic segment	6	2 (33)	2 (33)
Perforation of membrane	3	3 (100)	0 (0)
Ramstedt pyloromyotomy†	2	2 (100)	1 (50)
Laparotomy†	1	1 (100)	1 (100)
Closure of stomach perforation†	2	2 (100)	2 (100)
Duodenojejunostomy†	1	1 (100)	0 (0)
Total	**72**	**33 (46)**	**23 (37)‡**

*Failures include cases of operative mortality and cases requiring reoperation.
‡Pyloric atresia overlooked at time of operation.
‡Determined for the 62 cases in which surgical intervention occurred.

first glance, this mortality appears inordinately high. However, five of the 11 deaths were associated with other important congenital anomalies. Even if one excludes these cases, the mortality and failure rates are unacceptable. In addition, the known tendency of patients with gastrojejunostomies to experience marginal ulceration makes this a less desirable approach.

Resection of the atretic segment was employed six times. There were two deaths, which represented the only failures. Resection would appear to be indicated in patients with a large cord or discontinuity, although it is technically a more difficult procedure than a bypass.

Side-to-side gastroduodenostomy or excision of the membrane with pyloroplasty was used 27 times, with a mortality of 15%. One patient survived following reoperation. We believe that either side-to-side gastroduodenostomy or excision of the membrane with pyloroplasty offers maximum opportunity to cure infants with pyloric atresia.

Miscellaneous procedures such as laparotomy, closure of gastric perforation, and duodenojejunostomy were misdirected or inadequate and doomed, therefore, to failure. In all instances, these infants either died or required another procedure.

CONCLUSION

A case of complete solid atresia of the pylorus was treated successfully with side-to-side gastroduodenostomy, bringing to 81 the number of reported cases. The mortality in treated cases is 37%. Early, accurate diagnosis as well as adequate relief of the obstruction are the cornerstones of successful management. Either side-to-side gastroduodenostomy or excision of the membrane with pyloroplasty offer the lowest mortality and the greatest opportunity for success.

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Intraspinal Enterogenous Cysts

A Case Report and Review of Pediatric Cases in the Literature

Gregory L. Holmes, MD; Sharon Trader; Panos Ignatiadis, MD

• A patient with an intraspinal enterogenous cyst is described. A review of the English literature disclosed 26 previous pediatric cases reported. These cases were studied in regard to clinical presentation, laboratory findings, histology of the lesion, and neurological follow-up. Although rare, enterogenous cysts should be considered where there is evidence of spinal cord compression.

(*Am J Dis Child* 132:906-908, 1978)

Although rare, intradural cysts compressing the spinal cord are well-known entities. However, descriptions and discussions of these cysts in the English pediatric literature have been few. It is the purpose of this communication to report a case of an intraspinal enterogenous cyst and review previous pediatric cases reported. Since early detection of these lesions with subsequent neurosurgical decompression may lead to complete neurological recovery, it is important for the pediatrician to remain aware of this entity.

REPORT OF A CASE

This was the first hospital admission for this 13-year-old right-handed boy who was in his normal state of excellent health until approximately five months prior to admission when, while exercising, he dropped a weight-lifting bar on his chest. Several days after this episode, the patient developed paresthesias in his upper chest and back in a band-like distribution. The paresthesias occasionally became sharp and painful, but usually were described as a "pins and needles" sensation. He gradually developed paresthesias in his arms and eventually in his legs; two months prior to admission he noted left leg weakness. The pain increased in his chest and back and was exacerbated with coughing or straining at stool. Approximately one month prior to admission, the patient began to complain of difficulty with initiation of urination. The remainder of his medical history was unremarkable.

On admission the patient's general medical examination gave findings entirely within normal limits. On neurological examination, cranial nerves I through XII were normal except for slight, unsustained bilateral horizontal nystagmus on lateral gaze. On motor examination the patient had normal upper extremity bulk and strength. There was moderate bilateral weakness, greater on the left, and increased tone in the lower extremities. The muscle stretch reflexes in the upper extremities were normal. The lower extremities were hyperreflexic with bilateral clonus at the ankles. Extensor plantar responses were present bilaterally. Sensory testing demonstrated decreased vibratory, position, temperature, and light touch sensation below the T-1 level. Abdominal reflexes were absent. Cerebellar function was normal.

Cervical spine and thoracic spine roentgenograms were normal. A myelogram demonstrated at the T-1 level a large, well-defined, smooth anterior filling defect on the right side with displacement of the spinal cord to the left and posteriorly at that level (Fig 1). The appearance was one of an intradural, extramedullary lesion. Opening pressure was 120 mm H_2O. The spinal fluid contained one RBC per cubic millimeter, no WBCs, a protein concentration of 43 mg/dl (normal, 20 to 40 mg/dl), and a glucose concentration of 54 mg/dl.

The patient was taken to the operating room, where a total laminectomy was performed. The C-7, T-1, and T-2 spinous processes and lamina were removed. The dura was incised after inspection disclosed no evidence of an extradural mass. A blue, dome-appearing cyst was identified between the T-1 and T-2 posterior ramae on the right side; this was incised. Fluid drained spontaneously and the laterally displaced spinal cord returned to its normal position. The cyst itself was attached to the spinal cord anteriorly and laterally; an attempt was made to remove the wall, but this was unsuccessful since the wall was quite hardened anteriorly and there was fear of damage to the cord.

Pathological examination disclosed an enterogenous cyst. The wall of the cyst was made up of connective tissue lined with both cuboidal and squamous epithelium. Mucicarmine stain demonstrated mucin deposits (Fig 2).

The patient was seen two months following surgery. At that time he was symptom free and the neurological examination gave entirely normal findings.

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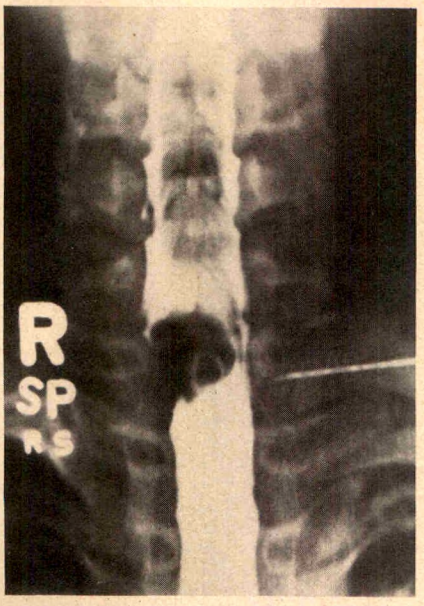


Fig 1.—Myelogram demonstrating extramedullary intradural lesion at T-1 area.

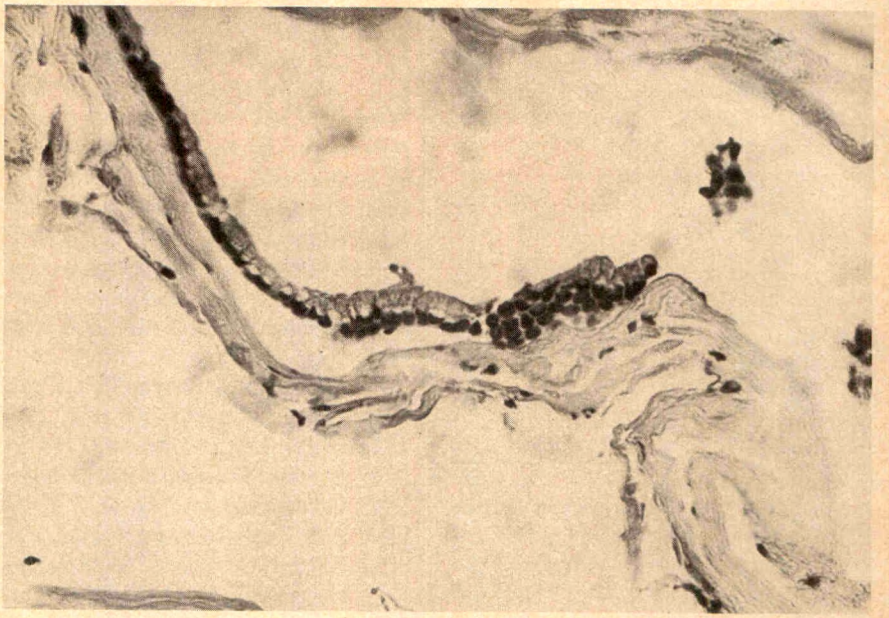


Fig 2.—Enteric cyst. Area of squamous epithelium on connective tissue base (original magnification ×150).

COMMENT

Intraspinal cysts encompass a wide variety of structural lesions.[1] There appears to be a continuum from simple arachnoid cysts on one end of the spectrum to highly complex teratomata at the other. All can lead to spinal cord compression. Arachnoid cysts, believed to arise from congenital faults in the distribution of the arachnoid trabeculae, are composed of normal or slightly thickened arachnoid filled with clear, colorless fluid that is probably CSF.[2,3] Epidermoid cysts have a convoluted and irregular connective tissue capsule lined by squamous epithelium. The wall of a dermoid cyst is similar, but also exhibits dermoid appendages such as hair follicles, sebaceous glands, and occasional sweat glands. The lumen of an epidermoid cyst is characterized by a waxy, white, keratinized debris shed by the epithelial lining, while the material found in the dermoid cyst contains in addition hair and glandular secretions that often give it a yellowish color and buttery consistency.[4] Ependymal cysts are thin-walled structures composed of connective tissue lined by a single layer of flat or papillary epithelium consisting of ciliated or nonciliated cuboidal or columnar cells that resemble ependymal cells. They are differentiated from simple neurenteric or enterogenous cysts by the absence of mucin.[1]

Neurenteric intraspinal cysts are lined by an epithelium specifically resembling that of respiratory or intestinal mucosa. The complexity of neurenteric cysts varies, from cysts of epithelium lying on a basement membrane supported by a layer of vascular connective tissue to cysts having multiple components including cartilege, bone, elastic fiber, fat, etc, and are referred to as teratomas by some authors.[1,5,6] Our patient's cyst was lined by cuboidal epithelium that, with the muscarmine stain, demonstrated mucin. As in a case reported by Hoefnagel et al,[5] areas of squamous epithelium were noted in the wall of this cyst. Characteristically, as in this patient, the thin-walled cysts are transparent, have a light-blue tint, and contain a clear, colorless fluid.

In order to increase our understanding of this entity, all cases of pediatric enteric intraspinal cysts in the English literature in which adequate clinical histories, neurological findings, and pathological information were provided were reviewed.[6-24]

A total of 26 cases were found. There were 18 males and 8 females; the average age for each sex was similar (males, 4 years and 8 months; females, 4 years and 7 months) and the range varied from newborn to 20 years. A summary of the cases follows.

Spinal Cord Region	No. of Patients
Cervical	7
Thoracic	6
Cervical-thoracic	5
Lumbar	4
Thoracic lumbar	2
Sacral	0
Lumbar sacral	2

One of the first symptoms was pain, a prominent symptom in 18 of the 26 children. The pain was usually referred to the area of the spinal axis where the cyst was located. The cyst can occur anywhere along the spinal cord; the frequency of the locations is given in the Table. Frequently, the diagnosis was made months after the initial onset of symptoms. As might be expected, other symptoms were related to the location and degree of spinal cord compression. The cysts were all extramedullary, intradural, and led to paralysis, increased deep tendon reflexes, plantar flexor responses, bladder dysfunction, and sensory loss. Nerve root involvement was rare; no cases were found where the neurological deficits were referable to the nerve roots only.

Associated congenital defects were

Clinical and Pathological Data of 26 Patients With Intraspinal Enterogenous Cysts*

	No. (%) of Patients
Symptoms	
Pain	18/26 (69)
Weakness	15/26 (58)
Neurological findings	
Hyperreflexia	15/26 (58)
Extensor plantar responses	9/26 (35)
Sensory abnormalities	5/26 (19)
Weakness	18/26 (69)
Pathology	
Type 1	10/26 (40)
Type 2	13/26 (50)
Type 3	3/26 (12)

*Eighteen males (average age, 4 years and 8 months) and eight females (average age, 4 years and 7 months).

numerous. Fourteen of 26 children (54%) had associated spinal defects. Seven had occult spinal bifida, five had gross bony defects such as hemivertebrae or spondylolisthesis, and two had the Arnold-Chiari malformation. In addition, on routine spine roentgenograms, ten of the children had features of an intraspinal expanding mass as evidence by absorption of lamina, widening of the neural canal, and scoliosis or kyphosis. Overall, 20 of 26 children (77%) had an abnormality on spinal roentgenograms. The diagnosis of a spinal cord mass was confirmed by myelography in 11 of 26 children (42%). However, a number of cases were reported prior to the widespread use of myelography. Myelograms usually showed evidence of an intradural, extramedullary block, either complete or partial. Spinal fluid examinations were reported in 16 children. Twelve of 16 (75%) children had elevated protein levels, with glucose concentration and blood cell counts usually normal. Evidence of spinal cord block with cessation of CSF flow at the time of the lumbar puncture was noted by four authors.

Definitive diagnosis can be made only when tissue is obtained at the time of surgery. The cyst is most frequently dorsal to the spinal cord. This was the case in 14 of 20 patients (70%) on whom this was commented on by the authors. In reviewing the pathology of these cases we used the nomenclature used by Wilkins and Odom.[1] Type 1 cysts were those lined by single pseudostriatified cuboidal or columnar epithelium with or without cilia, lying on a basement membrane, and supported by a layer of vascular connective tissue with scattered collections of WBCs. Type 2 cysts were similar to type 1 cysts, with the addition of mucous glands, serous glands, smooth muscle, striated muscle, fat, cartilege, bone, elastic fibers, lymphoid tissue, or nerve ganglion. Type 3 cysts were similar to type 2 cysts, with the addition of ependymal and glial tissues. Ten children had type 1 cysts, 13 had type 2, and three had type 3.

In reviewing the data it was noted that those cases with types 2 and 3 were more likely to be associated with other anomalies such as hydrocephalus, the Arnold-Chiari malformation, or myeloceles. Only two of ten cases of type 1 cysts had other defects, whereas ten of 13 type 2 and two of three type 3 cysts were affected by other anomalies.

Even though a portion of the cyst wall frequently remains after surgery, recurrence risk is quite small. Only one patient in this series had a recurrence.

There were five deaths, secondary to meningitis or other associated congenital defects. Twenty of 26 children reviewed had minimal or no neurological deficits six months to several years after operation.

The embryology of the development of such cysts has been discussed at great length in the literature and will not be dwelt on in this publication.[25-27]

Enteric cysts of the spinal cord should be considered in all cases in which there is clinical evidence of spinal cord compression. Fortunately, with early removal the prognosis is excellent.

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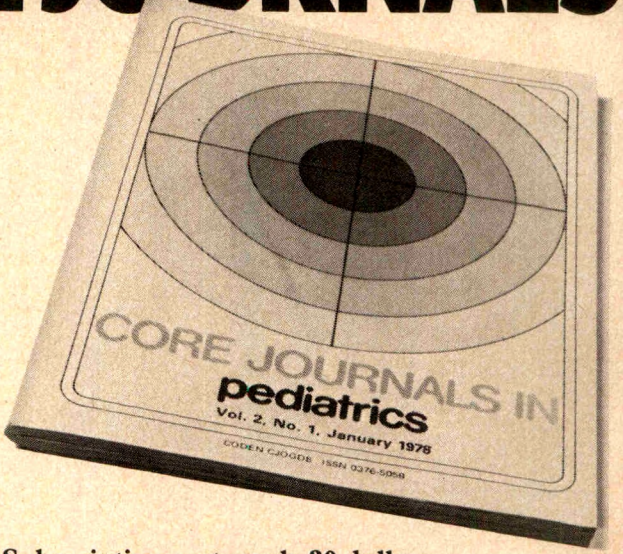
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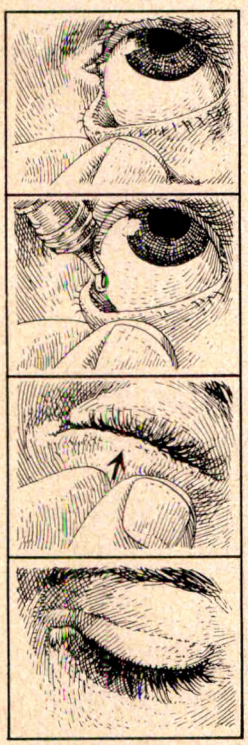
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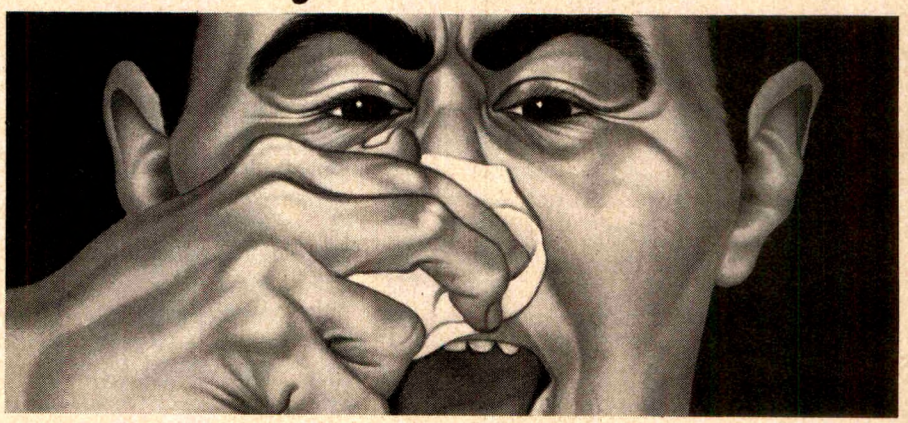
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Contraception

Daniel R. Mishell, Jr, MD

The steroid oral contraceptive is the most widely used method of contraception. Between 1965 and 1970, use of the oral contraceptive steroids increased from 24.4% to 35.4% of all married couples practicing contraception, and in 1975, the figure was 34.3%. In 1975, one of four of all married women in the United States younger than 45 years of age used oral contraceptive steroids. Their use is much more popular among women married less than five years, being used by 64.8% of these women, whereas only 10.4% of those married more than 20 years used oral contraceptive steroids. Among married women intending to have more births, 59.5% are users, whereas only 24.1% of women intending no more births are users.

There were originally three major categories of oral steroid contraceptives: combination, sequential, and daily gestagen. The combination is the most widely used and most effective type. It consists of tablets containing both an estrogen and a gestagen given continuously for three weeks. The sequential type, which is no longer marketed, consisted of estrogen alone for about two weeks followed by one week of combination estrogen and gestagen. With both these types, no medication is given for one week of four to allow for withdrawal bleeding. With the third method, a small dose of gestagen without estrogen is ingested every day.

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PHARMACOLOGY

Presently used oral contraceptives are formulated from synthetic steroids. There are two major types of synthetic gestagens: derivatives of 19-nor testosterone and derivatives of 17 α-acetoxy progesterone. This latter group of C-21 gestagens consisting of steroids, such as medroxyprogesterone acetate and megestrol acetate are not used in present contraceptive formulations.

In contrast to the 19-nor testosterone derivatives, when the C-21 gestagens were given to female beagle dogs, an increased incidence of mammary cancer developed in the dogs. Thus, all of the oral contraceptive formulations now available in the United States consist of varying dosages of one of the following five 19-nor testosterone gestagens: norethynodrel, norethindrone, northindrone acetate, ethinyldiol diacetate, or norgestrel (Fig 1). With the exception of two daily gestagen formulations, the gestagens are combined with varying dosages of two estrogens, ethinyl estradiol and ethinyl estradiol-3-methyl-ether (mestranol) (Fig 2). Each of these compounds has an ethinyl group in the 17-position. The presence of this ethinyl group enhances the oral activity of these agents as their essential functional groups are not as rapidly hydroxylated and then conjugated as they initially pass through the liver via the portal system, in contrast to what occurs with the naturally occurring steroids. The synthetic steroids thus have greater potency per unit weight than the natural steroids when both are ingested orally.

The various modification in chemical structure of the different synthetic gestagens and estrogens also alter their biological activity. Hence, one cannot compare the pharmacologic activity of the various gestagens or estrogens present in the particular contraceptive steroid only on the basis of amount present in the formulation. The biological activity of the various steroids has also to be considered.

Using human endometrial response as an endpoint, the gestagens, norethindrone and norethynodrel, are approximately equal in activity, whereas norethindrone acetate is twice as active. Ethinyldiol diacetate is 15 times as potent and norgestrel is about 30 times as potent as an equivalent weight of norethindrone. The two types of estrogenic compounds present in oral contraceptives, ethinyl estradiol and ethinyl estradiol-3-methyl-ether, or mestranol, also have

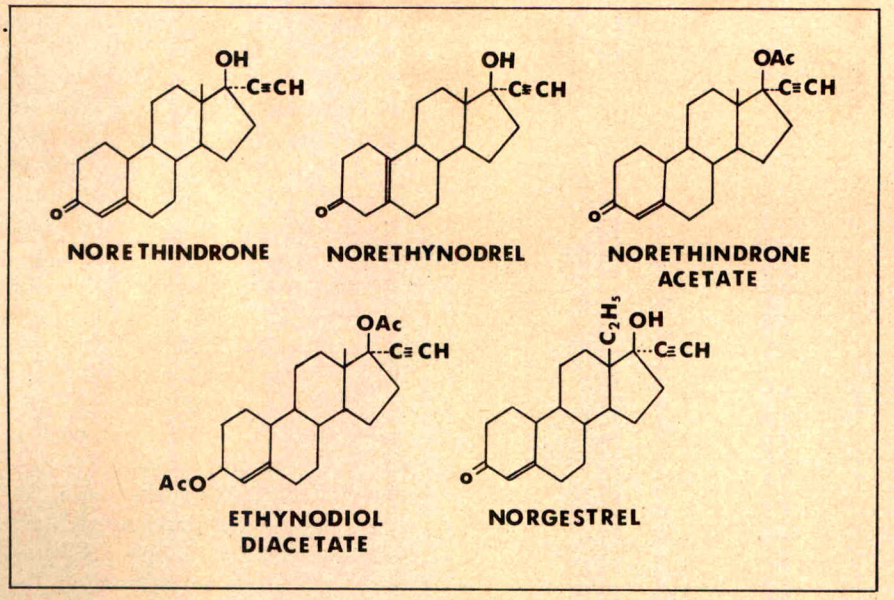


Fig 1.—Formulas of five gestagens used in combination oral contraceptives in United States.

different biological activities in the human.

To become biologically effective, mestranol has to be converted by demethylization to ethinyl estradiol and then to ethinyl estradiol sulfate. The rate of conversion varies among individuals; some are able to convert mestranol completely, others convert only half of it. Thus, in some individuals an equivalent weight of mestranol is as potent as the same weight of ethinyl estradiol, whereas in others it is only about half as potent. Overall, it has been estimated that ethinyl estradiol is about 1.7 times as potent as an equivalent weight of mestranol using human endometrial response and effect on serum levels of corticosteroid binding globulin production as endpoints. When deciding which contraceptive steroid to initially prescribe, it is important to evaluate both the quantity and biological activity of both steroid components of the formulations.

PHYSIOLOGY

Mechanism of Action

The combination oral contraceptive is the most effective type of oral contraceptive because these preparations consistently inhibit the midcycle gonadotropin surge, and thus, prevent ovulation. In addition, these drugs alter the cervical mucus, making it consistently thick, viscid, and scanty in amount and thus retarding sperm penetration. They alter motility of the muscle of the uterus and oviduct, thus altering transport of both ova and sperm. Furthermore, they act to decrease endometrial glycogen production so that less energy is available for the blastocyst to survive in the uterine cavity. Finally, they alter ovarian responsiveness to gonadotropin stimulation. Nevertheless, neither gonadotropin production or ovarian steroidogenesis is completely abolished and the levels of those endogenous hormones in the peripheral blood during ingestion of combination oral contraceptives are similar to those found in the early follicular phase of the normal cycle[1] (Fig 3 and 4).

Contraceptive steroids mainly prevent ovulation by interfering with gonadotropin releasing hormone (GnRH) release from the hypothalamus. Studies also show that the majority of women who had been ingesting combination contraceptive steroids had subnormal release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) after GnRH infusion, indicating that the steroids have a direct inhibitory effect on the pituitary as well as the hypothalamus. It is not known whether the amount of pituitary suppression is related to the syndrome of post-oral contraceptive amenorrhea.

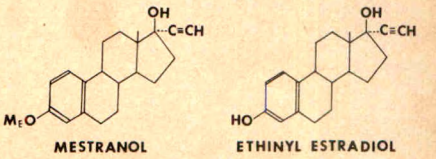


Fig 2.—Formulas of two estrogens used in combination oral contraceptives in United States.

The sequential and daily gestagen preparations do not consistently inhibit ovulation. Although they exert their contraceptive action via the other aforementioned mechanisms, because of the inconsistent ovulation inhibition, the effect of these two preparations is substantially less than with the combined type.

The combined type of oral contraceptive is the most effective type of contraception currently available. Although there has been no substantial difference in clinical effectiveness demonstrated among the various combination formulations available, those containing only 20 μg of ethinyl estradiol seem to be slightly less effective. Provided no tablets are omitted, the pregnancy rate is less than 0.2% per 100 women at the end of one year with the use of all formulations.

METABOLIC EFFECTS

Both the estrogen and gestagen components of the oral contraceptives have many other actions that affect nearly every organ system of the body. Some 52 metabolic alterations have been reported in those who use oral contraceptives. Patients taking these medications frequently experience undesirable symptoms in addition to the prevention of conception.

Although unwanted symptoms associated with oral contraceptive therapy are not infrequent, the incidence of serious complications is relatively rare, making the definitive establishment of a causal relation rather difficult. In most instances, a relation has been inferred from a series of case reports followed by a retrospective case control cohort analysis.

After two years of planning, in 1962, the Royal College of General Practitioners of Great Britain began a large scale prospective study of the health of those who use oral contraceptives, involving 1,400 physicians,

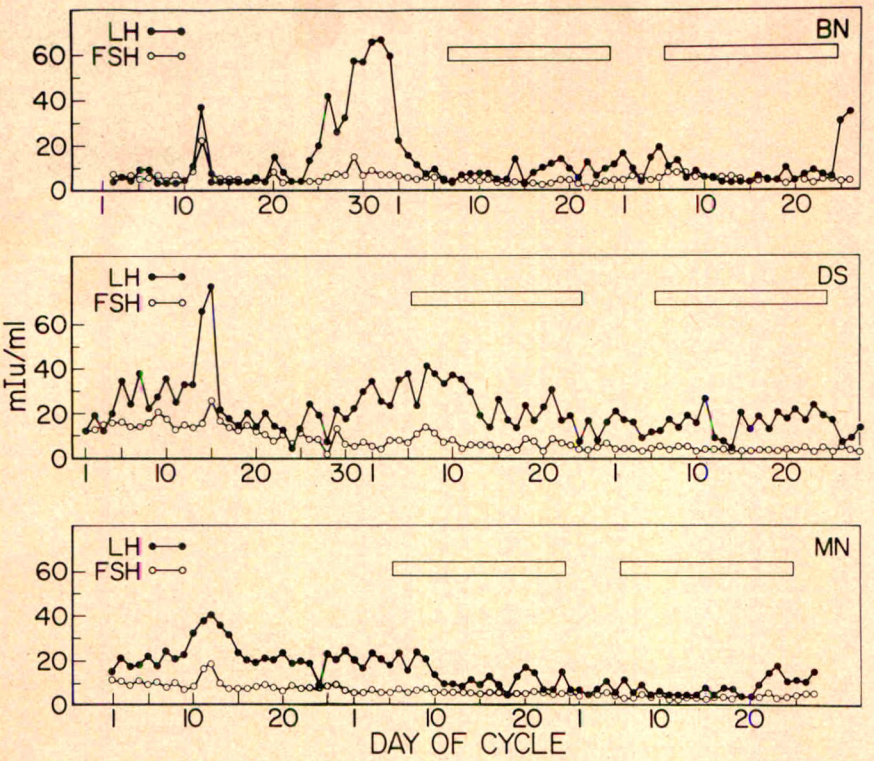


Fig 3.—Daily serum luteinizing hormone and follicle stimulating hormone levels in three subjects for three cycles. First cycle served as control and last two were treatment cycles with combination oral contraceptive. Hortizontal bars indicate days when steroid was ingested.

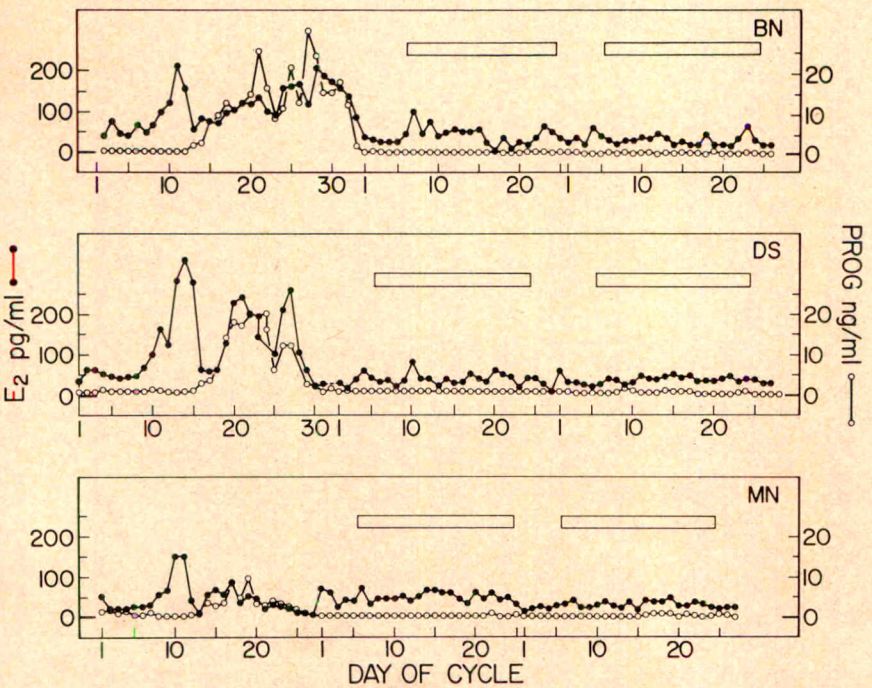


Fig 4.—Daily serum estradiol (E_2) and progesterone (PROG) levels in same three subjects as in Fig 3.

23,611 women who use oral contraceptives, and 22,766 controls. An interim report of the first five years of this study was published in 1974.[2] Another prospective study, involving 17,032 women in 17 family planning clinics in Great Britain was instituted in 1968. About half the women used oral contraceptives with the remainder approximately equally divided among the intrauterine device (IUD) and the diaphragm. The results of the first five years of this study were published in 1976.[3] The results of these two prospective studies are in agreement with nearly all the retrospective case control studies. For convenience, the effects of oral contraceptives have been classified into the following three categories: (1) effects on the primary target organs of the female reproductive system, (2) general metabolic effects, and (3) effects on other organ systems.

Effects on Organs of Female Reproductive System

Ovary.—Stromal fibrosis has been reported. It is usually transitory, disappears after contraceptives are stopped, and is of no clinical importance.

Myometrium.—Leiomyomata may enlarge on occasion with oral contraceptive use, but it is uncommon for them to enlarge to an extent that they become symptomatic. Nevertheless, the presence of leiomyomata constitutes one of the relative contraindications to the use of contraceptive steroids, and women with leiomyomata should be examined at frequent intervals, usually every three months. Since the progestogenic component diminishes the synthesis of the intrauterine estrogen receptor protein, the estrogen mitogenic effect on the cells of leiomyoma is usually slight.

Endometrium.—Alterations occur in the endometrium so that hypomenorrhea, amenorrhea, or lack of withdrawal bleeding may occur as well as intermenstrual bleeding. Usually, these symptoms are caused by insufficient estrogen or excessive progestogen, and can be ameliorated by increasing the estrogen/progestogen ratio. The steroids in the oral contraceptive produce these effects directly

on the endometrium rather than via the hypothalamic-pituitary axis.

Amenorrhea in women using oral contraceptives is only of concern because it cannot be differentiated from pregnancy. Oral steroids should not be ingested during pregnancy due to a reported increased incidence of fetal malformations. Therefore, it is best to induce regular withdrawal bleeding in women taking oral contraceptives by increasing the estrogenic component or using a less potent gestagen. If a woman has a gradual decrease in withdrawal bleeding followed by amenorrhea, the endometrium can be built up by adding 20 μg of estradiol to the previously used formulation for a period of about three months. Withdrawal bleeding will usually be reinstated. If a woman with regular withdrawal bleeding suddenly fails to have withdrawal bleeding, the oral contraceptive should be stopped and a sensitive pregnancy test performed.

Cervix.—A polypoid hyperplasia of the endocervical glands has been noted in those who use oral contraceptives. Although its appearance has some features that are similar to that of adenocarcinoma of the endocervix, this change is not malignant or premalignant. There is no evidence that oral contraceptives cause an increased incidence of epidermoid carcinoma of the cervix or carcinoma in situ. It has been reported that patients who chose oral contraceptives have a higher incidence of abnormal cervical cytology than women who chose other types of contraception, but the abnormal cytology has not been shown to be causally related to oral contraceptive use.

Vagina.—There have been numerous reports of bacterial changes in the vagina with an increase of vaginitis, especially moniliasis, in women receiving contraceptive steroids. If recurrent monilial vaginitis develops in those who use oral contraceptives, a glucose tolerance test should be performed.

Breasts.—There is an increased incidence of breast tenderness, mainly related to the estrogenic component of the oral contraceptive. In addition, milk production is diminished and the concentration of milk proteins and fats is reduced. The steroids are also found in measurable amounts in the milk of lactating women. The long-term effect of these steroids on the developing infant is not known. Oral contraceptives are, therefore, not advised for patients who wish to breast-feed their infants. Development of galactorrhea is also an uncommon side effect. Serum prolactin levels are slightly increased in those who use oral contraceptives.

Thus far, there has been no evidence of an increase in malignant breast disease in those who use oral contraceptives. In addition, there is evidence that the incidence of benign breast disease, mainly fibrocystic disease, is reduced and that this reduction is directly related to the dose of gestagen in the product.[4] This is most probably related to the inhibition of synthesis of the intracellular estrogenic receptors by the gestagen component of the oral contraceptive.

Hypothalamus.—The incidence of amenorrhea for more than six months after discontinuing the use of oral contraceptives ranges from 0.2% to 0.8%. The incidence is higher in patients who have oligomenorrhea or amenorrhea prior to starting oral contraceptive therapy.[5] Thirty-five percent to 41% of women in whom amenorrhea develops after taking oral contraceptives have a prior history of menstrual irregularity. It is not known whether post-oral contraceptive amenorrhea is caused by continued suppression of the hypothalamic-pituitary axis or whether the periodic withdrawal bleeding produced by oral contraceptives serves to mask an amenorrheic state that would have occurred if the steroids were not ingested or whether both mechanisms occur. In any event, the use of any oral contraceptive steroid is contraindicated for patients who have oligomenorrhea or amenorrhea.

If individuals with amenorrhea or oligomenorrhea desire regular menses, treatment with a gestagen alone for five days each month is usually sufficient to induce menses without suppressing hypothalamic function or masking the development of amenorrhea associated with low estrogen production. If these women desire contraception, it is best to use either a barrier method or a copper IUD. Post-oral contraceptive amenorrhea may also develop in women with a previous history of regular menses.

If the amenorrhea persists for more than six months, routine diagnostic procedures should be undertaken to determine the cause since a higher percentage of women with post-oral contraceptive amenorrhea have galactorrhea (50%), increased prolactin levels (50%), and evidence of a pituitary microadenoma (25%). Induction of ovulation with clomiphene citrate is less successful in women with post-oral contraceptive amenorrhea than in women with amenorrhea not associated with oral contraceptive use.

General Metabolic Effects

Serum Proteins.—In addition to a general decrease of blood amino acid levels similar to that seen in pregnancy, there are changes in blood protein concentration similar to those occurring in pregnancy but of less magnitude. Thus, there are increases in the levels of α-2 and β-globulins blood coagulation factors and the carrier proteins: cortisol-binding globulin, thyroid binding globulin, transferin, and ceruloplasmin. The pre-β-lipoprotein and haptoglobin levels are also increased whereas albumin levels are decreased. These changes are due mainly to a direct effect of estrogen on the endoplasmic reticulum of the liver that results in altered protein production. These changes, for the most part, do not represent a medical hazard but they do alter the results of some laboratory tests. Thus, serum levels of copper and iron will be increased while tests of thyroid function will be altered to the same extent that occurs in pregnancy.

In contrast, there is a slight but definite increase in the free as well as the bound plasma cortisol level. The increase in free cortisol may contribute to a number of side effects of the oral contraceptives, such as fluid retention, headache, hypertension, and mood changes. The aforementioned protein changes have been shown to be responsible for two

important clinical effects.

Thromboembolism.—Studies by Vessey et al[3] in England and Sartwell[6] in the United States, showed a small but substantial increase in thromboembolic disease in those who use oral contraceptives. Mortality from thromboembolic disease associated with the use of hormonal contraceptives is estimated to be about three per 100,000 women a year. Results from these retrospective studies were confirmed by the British prospective studies. A causal relation between use of oral contraceptives and thromboembolism has thus been definitely established. The Royal College study indicated that the development of thromboembolic disease was related to age, but not to parity, to smoking, and to the duration of oral contraceptive use.

The cause, in addition to the increase in blood clotting factors aforementioned, is due to an increase in the number of platelets as well as platelet adhesiveness and a decrease in antithrombin-3. All these changes are produced by the estrogenic component of the formulation. There is evidence that the increased incidence of thromboembolism is related to the amount of estrogen; therefore, it is best not to prescribe oral contraceptives with more than 50 μg of estrogen unless it is absolutely necessary for short intervals to prevent breakthrough bleeding. There is no evidence that the incidence of thromboembolism has increased in women with varicosities of the lower extremities. Individuals in whom chest pain develops while taking contraceptive steroids, should discontinue therapy as well as have further diagnostic studies, including a lung scan.

Hypertension.—One of the α-2-globulins whose serum level is increased, is angiotensinogen, a plasma renin substrate. In certain individuals without a normally functioning feedback mechanism, plasma renin and angiotensin levels are also increased and therefore, a substantial but reversible hypertension develops shortly after initiating therapy.[7] The incidence of hypertension developing in normotensive women after treatment with oral contraceptives is relatively low. Since these women cannot be identified in advance, all individuals treated with oral steroids should have regular monitoring of their blood pressure. A larger proportion of women with preexisting hypertension may have a further increase in blood pressure with oral contraceptive therapy and thus, the presence of preexisting hypertension constitutes a relative contraindication to their use.

The Royal College prospective study estimated that the incidence of hypertension in the first year of oral contraceptive use is less than 1%, but showed that there was a relation between the duration of oral contraceptive use and the development of hypertension. Data from this study indicated that in about 5% of oral contraceptive users hypertension develops after five years of usage, an incidence 2.6 times greater than controls.

Carbohydrate Metabolism.—Impairment of glucose tolerance and an increase in plasma insulin levels have been reported in oral contraceptive users, although it has not been definitely established whether these changes are related to the estrogen or the gestagen component of the formulation, or both.[8] Therefore, it is not advisable to prescribe oral contraceptives for patients who have had a previous abnormal glucose tolerance test, such as those with gestational diabetes. It is suggested that a glucose tolerance test be performed annually in all women receiving this type of contraceptive who are at risk to develop diabetes, eg, those with a family history of diabetes, large birth weight babies, unexplained fetal deaths, and obesity.

Lipid Metabolism.—Oral contraceptives often cause an increase in serum triglyceride and cholesterol levels. The increase in triglyceride levels seems to be mainly an estrogen effect. There is increasing evidence that there is an increased incidence of myocardial infarction in women older than 35 years of age, particularly those with associated risk factors, mainly heavy cigarette smoking.

Water and Electrolyte Metabolism.—Although the mechanism is not understood, oral steroids cause a decrease of sodium excretion accompanied by water retention. Edema develops in some users and some have associated weight gain of 1 to 2.5 kg.

Body Weight.—Because gestagens in current formulations are chemically related to testosterone, they are anabolic and in some women there will be an increase in body weight beyond that due to retention of fluid. Thus, if a woman gains more than 5 kg in a year, oral contraceptives should be discontinued or a preparation containing a less potent gestagen should be used.

Tryptophan Metabolism.—Tryptophan is normally metabolized by two pathways, a major nicotinic acid, ribonucleotide sequence in the liver, and a minor serotonin sequence in the brain. The estrogenic component of the oral contraceptives diverts tryptophan from the minor to the major pathway and thus, causes lower serotonin levels in the brain. These low serotonin levels are associated with depression and sleep disturbances and it is thought that this mechanism explains some of the neuropsychiatric symptoms noted in oral contraceptive users. The British Royal College prospective studies confirmed the causal relation of oral contraceptives with neurotic depression. Certain of these metabolic changes in tryptophan metabolism are also noted in pyridoxine deficiency, and oral contraceptive users do have low serum levels of pyridoxine. Symptoms of depression in oral contraceptive users can be alleviated by treatment with pyridoxine (vitamin B_6), but it is best to discontinue the steroid medications if symptoms of depression develop.

Vitamins and Minerals.—In addition to pyridoxine, there are decreases in serum folic acid, calcium, manganese, and zinc, whereas ascorbic acid levels are increased in oral contraceptive users. The clinical importance, if any, of these changes is unknown at present, and routine vitamin supplements for oral contraceptive users have not been shown to be of benefit.

Effects on Other Organ Systems

Liver.—There is an increased incidence of abnormalities in some liver function tests in oral contraceptive users, mainly tests dealing with bile excretion, such as bromsulphalein

retention. The steroids adversely affect the function of enzymes aiding excretion of bile, similar to the changes that occur in pregnancy. Both a collaborative retrospective study in the United States and the prospective British studies indicate that oral contraceptive users have twice the risk of cholelithiasis developing as controls.[4] However, the actual numbers involved is small, being estimated to be 49 to 68 women per 100,000 users a year in the two studies. It has recently been shown that oral contraceptives alter the composition of gallbladder bile in women, mainly an increase in the concentration of cholesterol.

Those individuals who develop recurrent jaundice of pregnancy frequently develop jaundice when treated with oral contraceptive steroids, and their use is thus contraindicated in these individuals. Active liver disease is also a contraindication to hormonal contraceptive therapy, but their use need not be restricted in individuals with a history of hepatitis, who currently have normal liver function. Nevertheless, these individuals should have periodic tests of liver function at regular intervals after receiving oral steroids.

A rare complication is the presence of benign liver cell adenomas.[9] The actual incidence of these tumors, which can cause pain as well as rupture with intraperitoneal bleeding and rarely death is not presently known, but is probably less than one in 250,000 users. The presence of these tumors cannot be detected by changes in liver function but because they can become large, routine annual palpation of the liver should be performed in all women ingesting oral contraceptives. If an adenoma is suspected, its presence can be confirmed by a liver scan. After the steroids are stopped, most of these tumors undergo spontaneous regression.

Central Nervous System.—There is an increased incidence of nausea and vomiting as well as migraine headaches and cerebral vascular accidents in women receiving oral contraceptives. The incidence of nausea is thought to be related to the estrogen component and is greater in the first few cycles of use. Individuals with preexisting migraine headaches may undergo a time of occurrence change from the premenstrual phase of the untreated cycle to the medication-free interval after therapy. A recent retrospective collaborative study has estimated that the relative incidence of cerebral thrombosis in women who use oral contraceptives is about nine times greater than nonusers, whereas the risk of a cerebral hemorrhage developing is doubled.[4]

Although the incidence of this severe complication is extremely low, a definite causal relationship has now been established. Therefore, if an increased incidence of severe or migraine headaches or any peripheral neurological changes develop while patients are taking oral steroids, it is best to discontinue their use. Oral contraceptive use may increase the incidence of epileptic seizures in some women with epilepsy. Therefore, the presence of epilepsy is also a relative contraindication to oral contraceptives.

Skin.—Melasma, similar to that which develops in pregnancy, occurs in some patients. This change is accentuated by exposure to sunlight, takes a long time to disappear after stopping medication and there is no specific treatment. The gestagenic component of the combination contraceptive causes an increase in sebum production and acne, whereas the estrogenic component exerts an ameliorative effect. Therefore, in individuals with acne or those in whom acne develops with contraceptive steroid therapy, a formulation with a higher estrogen/gestagen ratio should be used.

Genitourinary.—There is a definite association between oral contraceptive use and urinary tract infection. Both pyelitis and cystitis were substantially increased in users compared with controls. The reason for this increased incidence of urinary tract infection is not established but may be due in part to increased sexual activity in oral contraceptive users.

Gastrointestinal Tract.—There are indications of an increased incidence of mesenteric thrombosis and possibly ulcerative colitis. Whether there is a causal relation between development of these entities and oral contraceptive use is doubtful according to the findings of the British Royal College studies. Nevertheless, patients in whom these disease entities develop while receiving oral contraceptive therapy should have the medication discontinued.

Eye.—Several adverse ophthalmologic effects, including retinal artery thromboembolism, have been reported. Again, no causal relation can be established and in two well-controlled studies no substantial differences in eye abnormalities were found between groups of women using oral steroids and those not taking the drugs.

Immune Phenomena.—The British Royal College study showed a substantial increase in frequency of gastric influenza, hay fever, and chicken pox in oral contraceptive users. This increased frequency was also found for other viral diseases and may be related to alterations in the immune mechanism brought about by oral steroid use.

Effect on Subsequent Fertility.—There is no evidence that use of oral contraceptives has an adverse effect on the outcome of subsequent pregnancies. In the British Royal College study, the total abortion rate in women stopping oral contraceptives to conceive was 13%, which is similar to the normal incidence of spontaneous abortion. No apparent difference in congenital abnormalities has been found in babies born to previous oral contraceptive users compared with a control population. There is some evidence however, that ingestion of oral contraceptives during pregnancy may increase the incidence of congenital limb and heart defects[10] as well as cause masculinization of the external genitalia of female fetuses. Therefore, women should not take oral contraceptives if they are pregnant or fail to have withdrawal bleeding, and a possibility of pregnancy exists.

Resumption of fertility after stopping oral contraceptive use is delayed in some women for some months. In the British Royal College study, 85% of nulliparous women and 93% of parous women had conceived within

two years. Since about 10% of couples in the general population are infertile, these data indicate that fertility after discontinuation of oral contraceptive use is not appreciably reduced.

One report has suggested that the incidence of chromosomal abnormalities is increased in spontaneous abortions occurring in women who have conceived shortly after discontinuing oral contraceptives,[11] but more recent studies have been unable to confirm this finding. Since the return of ovulation is delayed for variable periods of time after stopping oral contraceptives, it is difficult to estimate the expected date of delivery if conception takes place before spontaneous menses resumes. For these reasons, if women stop oral contraceptives to conceive, it is probably best that they continue to use barrier methods for about two to three months while they resume regular cycles.

CHOICE OF FORMULATION

It has been suggested that preparations with greater amounts of gestagens should be given to "estrogen dominant" women and vice versa. There are no data to demonstrate that the incidence of side effects is substantially reduced by such a treatment plan. Many of the common annoying side effects, such as nausea and breast tenderness, as well as the uncommon serious side effects, such as thromboembolism are related to the dosage of estrogen in the formulation.

Government regulatory agencies of several countries have reported that preparations containing 50 μg of estrogen or less are associated with a lesser incidence of thromboembolism. For these reasons, the Food and Drug Administration in 1970, recommended that "the practicing physician, in his choice of an oral contraceptive, consider that a product containing a lower dose of estrogen should be prescribed if it is otherwise effective and acceptable to the patient. The higher dose products should be reserved for use when necessary."

Although most of the serious adverse metabolic and clinical alterations are related more to the estrogen than the gestagen component of the formulation, some changes such as alterations in carbohydrate metabolism and hypertension may also be caused by the gestagenic component. In the British Royal College study, the incidence of both hypertension and gallbladder disease was correlated with gestagen dosage.

For these reasons, when deciding which contraceptive preparation to initially prescribe, it would seem prudent to use the formulation with the least potency (considering the potency per unit weight) of both estrogen and gestagen, that does not cause adverse symptoms of bleeding and amenorrhea.

Formulations containing gestagens alone obviously have a lower incidence of adverse metabolic and thromboembolic effects. Blood pressure is not affected, serum lipids are unchanged, nausea and breast tenderness are eliminated, and milk production and quality are unchanged. Despite these advantages, the serious disadvantages of a very high frequency of intermenstrual and other abnormal bleeding patterns, including amenorrhea, as well as a lower rate of effectiveness, considerably limit use of these agents. The actual failure rate of these preparations has been reported to vary between 2% and 8% a year, and a high percentage of these pregnancies are ectopic.

One possible indication for prescribing these preparations is the nursing mother who greatly desires to use oral contraceptives. Since these women have reduced fertility and are amenorrheic, the major disadvantages of these preparations are minimized. Nevertheless, a small portion of these synthetic steroids have been detected in breast milk and thus, are ingested by the infant. The long-term effects, if any, of these gestagens on the infant are not known.

It is best to use the combination oral contraceptive with the lowest effective dose and an acceptable level of side effects, namely one of the combinations containing 50 μg of estrogen or less. In the United States, there are seven products marketed with 50 μg of estrogen. Since 1975, an additional nine products that contain less than 50 μg of estrogen have been marketed. These nine products consist of six different formulations. The physician and patient must, therefore, decide whether to choose one of the oral contraceptives with 50 μg of estrogen or less. At the present time, one cannot make this decision on a truly rational basis because of the lack of sufficient clinical data.

On theoretical grounds formulations with less than 50 μg of estrogen should have certain benefits and certain disadvantages when compared with the formulations containing 50 μg. However, no studies have been published that compare metabolic alterations in women ingesting oral contraceptives with 50 μg of mestranol with those taking oral contraceptives that contain less than 50 μg of estradiol. These studies are extremely important as all the latter formulations contain ethinyl estradiol, which is about twice as potent as mestranol, the estrogenic component of several formulations containing 50 μg of estrogen.

The most serious side effect of the oral contraceptive is thromboembolism. A prospective British study showed that products with greater than 50 μg of estrogen had a higher incidence of thromboembolic phenomena than did the products containing 50 μg of estrogen. However, there is no evidence that any of the products with less than 50 μg have a lower incidence of vascular disease or other abnormal metabolic effects.

The theoretical disadvantages of lowering the dose of estrogen would be an increased incidence of irregular bleeding and also conception. If tablets were missed or delayed, ovulation could occur. In addition, because of the increased bleeding, some might not take the oral contraceptive regularly or might stop altogether and thus be at risk. One study of the formulation with 20 μg of estrogen suggests that it may have a slightly higher failure rate, but definitive comparative studies have yet to be performed. The incidence of breakthrough bleeding and spotting with the various preparations has been reported to range from 11% to 28%, in the second cycle of use, which is higher than the percentage reported with

higher doses of estrogen.

To obtain valid information concerning any clinical manifestation, such as irregular bleeding or use-pregnancy rates, randomized comparative studies must be performed. Until such time as the results of such studies are available, the clinician has to rely on the following facts: First, all of the combination products are theoretically equally effective, although the effectiveness of products with 20 μg of estrogen may be slightly lower. Second, those products with less than 50 μg of estrogen seem to have an increased incidence of abnormal bleeding. Finally, those products with greater than 50 μg of estrogen have an increased incidence of thromboembolism. Since the proportion of mestranol metabolized to ethinyl estradiol varies among individuals, it is probably best to initially prescribe formulations with 30 to 35 μg of ethinyl estradiol to obtain a more uniform response.

These formulations have potentially theoretical benefits since in some women ingesting 50 μg of mestranol all of this drug is metabolized to estradiol. If a preparation with 50 μg of estrogen is prescribed in an attempt to avoid potential bleeding problems, and estrogenic symptoms then develop, such as nausea or breast tenderness, the amount of estrogen may be decreased. If in patients receiving formulations with less than 50 μg of estrogen, breakthrough bleeding or amenorrhea develop, the estrogen dosage may be increased.

TIME TO START ORAL CONTRACEPTIVES

Adolescents

In deciding whether the pubertal, sexually active girl should use contraceptive steroids, the clinician should be more concerned about compliance than possible physiological harm. Provided the postmenarcheal girl has demonstrated maturity of the hypothalamic-pituitary-ovarian axis by having at least three regular, presumably ovulatory cycles, it is safe to prescribe oral contraceptives. As aforementioned, oral contraceptives should not be prescribed to women of any age with oligomenorrhea because of the increased chance that post-oral contraceptive amenorrhea will develop. One need not be concerned about accelerating epiphyseal closure in the postmenarcheal girl because her endogenous estrogens have already initiated the process prior to menarche.

There is a difference in the rate of return of ovulation and bleeding in the postabortal woman and after-term delivery. In the former, the first episode of menstrual bleeding is usually preceded by ovulation. At term, the first episode of bleeding is usually anovulatory. Ovulation occurs sooner after an abortion, usually between two and four weeks, while the delay is usually four to six weeks after a term delivery.

In women who have an abortion in the first trimester, oral contraceptives should be started immediately. In those who deliver after 28 weeks and are not nursing, the combination oral contraceptive should be started two weeks after delivery. If pregnancy ends between 12 and 28 weeks, contraceptive steroids should be started one week after delivery. The reason for delay in the latter instances is that the normally increased risk of postpartum thromboembolism may be increased by steroids.

SAFETY, CONTRAINDICATIONS, AND PATIENT MONITORING

In assessing the safety of oral contraceptives, as well as other methods of contraception, the potential harmful effects of unwanted pregnancy must be considered. The risk of morbidity and death associated with therapeutic abortion as well as pregnancy in the woman younger than 40 years of age, is greater than that associated with hormonal contraceptive use. The USFDA has decided that oral contraceptives are safe, inasmuch as their benefits outweigh their risks.

Nevertheless, there are certain contraindications. The USFDA lists the following six absolute contraindications: estrogen dependent neoplasia; cancer of the breast; active acute or marked chronic liver disease with abnormal function; a history of thrombophlebitis, thromboembolism, or thrombotic disease, including cerebral vascular and coronary artery disease; undiagnosed abnormal uterine bleeding; and pregnancy. Additional contraindications, such as congenital hyperlipidemia, diabetes mellitus, history of gestational diabetes, and hypertension should be added to this list. Relative contraindications include, depression, migraine headache, leiomyomata of the uterus, epilepsy, oligomenorrhea and amenorrhea. Patients with these conditions who ingest oral contraceptives should be seen at frequent intervals, at least every three months.

In addition, all individuals receiving these potent pharmaceutical agents should be seen by a physician and examined regularly, at least three months after initiating therapy and annually thereafter. Prior to starting therapy, as well as during these intervals, a pelvic examination should be performed, the patient's blood pressure and weight recorded, and the breasts examined. Assays of fasting serum triglyceride and cholesterol should be performed in women younger than 60 years of age, with a family history of myocardial infarction and a fasting blood glucose should be obtained in women with a family history of diabetes. By performing these routine examinations in all women, one can hopefully avoid some of the serious, but uncommon, side effects. There are no documented benefits derived from intermittent stopping of therapy, and there is a risk of unwanted pregnancy.

It seems now that the incidence of myocardial infarction in oral contraceptive users is considerably increased almost threefold only if certain risk factors are present.[12,13] The major risk factor is heavy cigarette smoking, others are hypertension, hypercholesterolemia, and possibly diabetes and obesity.

Recent data obtained from both British prospective oral contraceptive studies, the Royal College of General Practitioners study, and the Oxford Family Planning Association study indicate that in addition to an increased risk of death from myocardial infarction, there is an increased risk of death from a wide variety of circulatory diseases in oral contracep-

tive users. The Royal College study indicated that the mortality rate for women who had ever used oral contraceptives was 4.7 times that of controls. For nonrheumatic heart disease and hypertension the death rate was 4.0 times that of controls and for cerebrovascular diseases, mainly subarachnoid hemorrhage, it was 4.7 times that of controls.

A similar increased incidence of death from cardiovascular diseases was observed in the oral contraceptive users in the Family Planning Association study.[14] Of the 43 total deaths in this study group, nine deaths from cardiovascular disease occurred in the oral contraceptive users and one in the IUD or diaphragm users. These findings support Beral's analysis of mortality trends in 21 countries.[15] This analysis showed that increases in mortality from all cardiovascular diseases in women aged 15 to 44 years have been strongly associated with changes in prevalence of oral contraceptive use in each country.

The Royal College study showed in addition that the excess mortality due to cardiovascular causes in women who had used oral contraceptives, increased with increasing age of the patient and with duration of oral contraceptive use, and was about threefold greater in women who smoked. Overall, the increased risk of death in women who had at some time used oral contraceptives was 20 per 100,000 women a year, which is more than ten times greater than the risk of death from pregnancy in controls, and twice as great as the risk of death from all accidents. The risk of death increased substantially in women older than 35 years of age and in women who had used oral contraceptives for more than five years. Furthermore, the increased risk of death occurred both in current users of oral contraceptives as well as those who had previously used oral contraceptives and stopped. The mortality was increased 4.9 and 4.3 times that of controls from those two groups, respectively. Since the metabolic changes occurring during oral contraceptive use generally regress within three months after stopping oral contraceptives, the findings of this study indicate that certain circulatory alterations may present for longer time periods.

With this information, it is now recommended that women older than 35 years of age should discontinue oral contraceptives and use another method, and that women younger than 35 years of age with hypertension, diabetes, and hyperlipidemia should not use oral contraceptives. Women who are heavy smokers should be strongly encouraged to either stop smoking or use another method of contraception.

The analysis of earlier data by Tietze et al[14] indicated that whereas with advancing age the risk of mortality with use of oral contraceptives increases, the risk of death from IUDs declines and with tubal sterilization remains low. Because of the increasing risk of death in older women using oral contraceptives as well as the increased incidence of systemic disease, oral contraceptives should be used mainly by young healthy women for the purpose of family spacing. Once childbearing is complete, alternative forms of contraception, mainly the IUD, should be used or sterilization for either member of the couple should be performed. Sterilization is now the most frequent form of preventing pregnancy in women who do not intend to have more children (43.5% in comparison with 24% for oral contraceptives). Women who wish to continue using oral contraceptives after their family is complete may continue to do so with careful monitoring, if they have no associated risk factors, but their use after the age of 35 years of age in all women should be discouraged.

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Radiological Case of the Month

Lionel W. Young, MD; Contributed by Gerald A. Mandell, MD, A. Edward O'Hara, MD

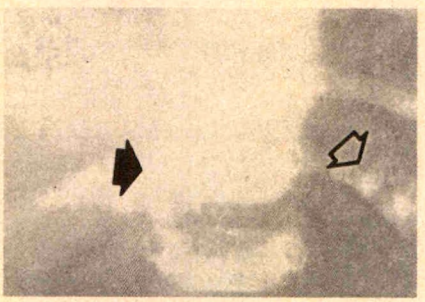
Clinical History.—A 5½-month-old infant was admitted to the Thomas Jefferson University Hospital because of persistent diarrhea for four weeks. The patient was the product of a full-term gestation and a vaginal delivery. The birth weight was 3,060 g. There was an uneventful neonatal course without history of anemia or jaundice.

Physical Examination.—Results of physical examination were unremarkable. Roentgenograms of the abdomen were obtained because of the gastrointestinal history (Fig 1 and 2). Subsequent evaluation included an intravenous urogram (Fig 3) and inferior vena cavogram (Fig 4). Findings from laboratory data, including catecholamines and titers for rubella and cytomegalic inclusion disease were negative.

From the Departments of Radiology, Hahnemann Hospital (Dr Mandell), and the Thomas Jefferson University Hospital (Dr O'Hara), Philadelphia.

Reprint requests to the Department of Radiology, Children's Hospital of Pittsburgh, 125 DeSoto St, Pittsburgh, PA 15213 (Dr Young).

Fig 1.



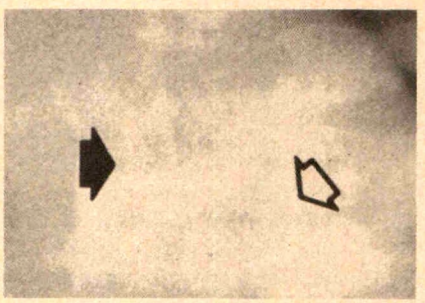


Fig 2.

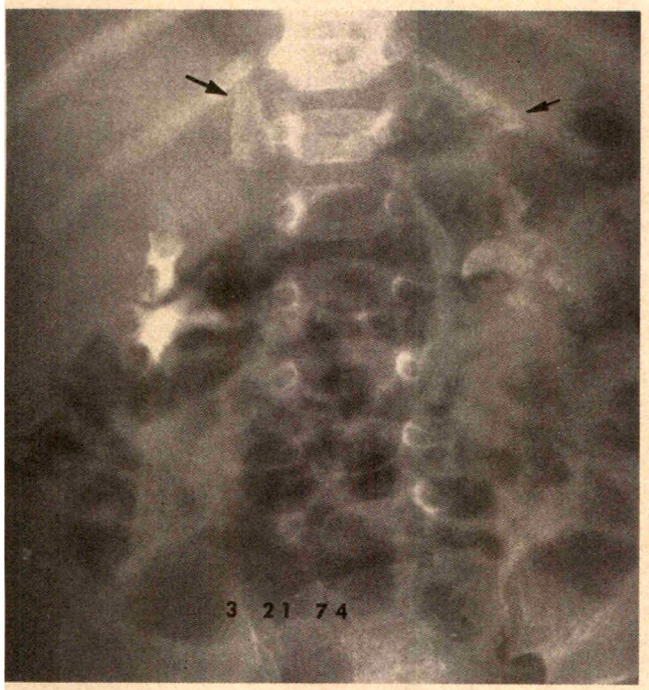


Fig 3.

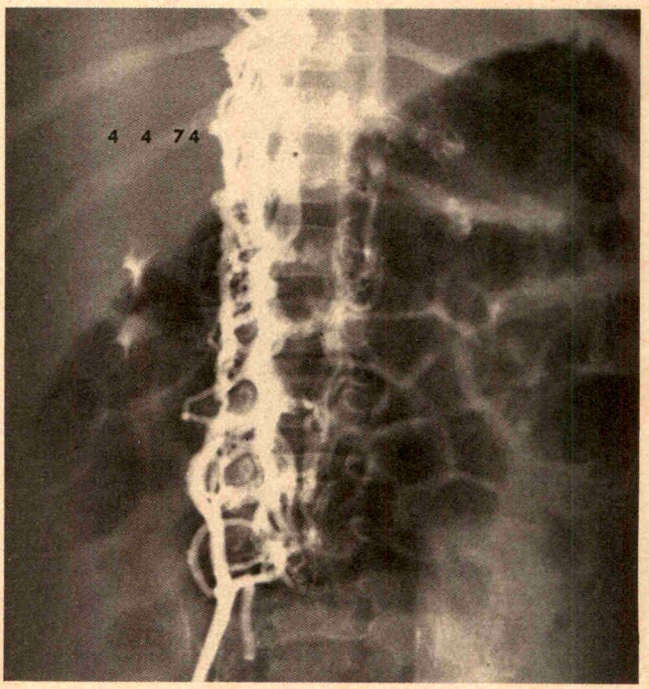


Fig 4.

Denouement and Discussion

Fig 1.—Bullet-shaped calcification on right side of T-12 (solid arrow). Discrete adrenal calcification to left of T-12 (open arrow).

Fig 2.—Bullet-shaped calcification anterior to T-12 in course of inferior vena cava (solid arrow). Adrenal calcification superimposed on vertebra T-12 (open arrow).

Fig 3.—Bullet-shaped calcification in right upper quadrant without renal displacement (arrow). Adrenal calcification in left upper quadrant above left kidney without renal displacement (arrow).

Fig 4.—Complete thrombosis of inferior vena cava with collateral venous drainage. Catheter placed in right external iliac vein.

Presumptive Benign Intra-abdominal Calcifications: Adrenal and Inferior Vena Caval

A bullet-shaped calcification appearing in the right upper quadrant of the abdomen is a rare finding, but quite characteristic of a thrombosis of the inferior vena cava. To our knowledge, eight cases have been reported in the literature. Infection, neoplasia in the area of the vena cava or liver, and structural anomaly of the venous conduit[1] may produce thrombosis. Thrombosis of the inferior vena cava is usually detected as an incidental finding.

Calcification of the adrenal gland is more common. In 1959, Jarvis et al[2] reported 26 cases diagnosed either roentgenographically or microscopically. Suprarenal calcifications have been reported in tuberculosis, Addison's disease, cysts, adrenal hemorrhage, and adrenal neoplasm. The most common neoplasms would be ganglioneuroma, neuroblastoma, adrenal carcinoma, and pheochromocytoma. In metabolic diseases, such as Niemann-Pick disease and Wolman's disease, the calcifications are usually bilateral. Calcifications occur in approximately 50% of the neuroblastomas and are usually stippled, fine, granular densities rather than the larger, discrete densities of adrenal hemorrhage.

The hemorrhage is initially outlined by a curvilinear rim of calcification with eventual coalescence of its central portions. The calcifications disappear with the passage of a number of years. The right adrenal gland is involved more frequently than the left, approximately 70% of the time. The right adrenal gland, resting between the liver and the spine is more subject to compression. The right adrenal vein takes off from the inferior vena cava and is more subject to pressure changes.

The adrenal glands at birth are normally quite large, approximately one third the size of the kidneys. Evidence of previous adrenal hemorrhage was found in 1% of the autopsy cases. The usual cause of adrenal hemorrhage is birth trauma that is associated with midforceps extraction, breech delivery, a very large infant, and an infant of low birth weight. Physiological involution is sometimes postulated as a cause. Massive hemorrhage into the adrenal gland with the additional components of thrombocytopenia and hypofibrinogenemia is usually fatal.

Our case illustrates the current appearance of two presumably benign calcifications in the same patient. During delivery, the 3,060 g size of the infant may have precipitated subclinical moderate hemorrhage into the left adrenal gland. Possibly transient stasis of blood from hypotension with reduction of vena caval blood flow resulted in vena caval thrombosis.

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The Editors welcome contributions to "Picture of the Month" and "Radiological Case of the Month." Those who wish to contribute should send their manuscripts to Dr Gellis (Picture of the Month), Boston Floating Hospital, 20 Ash St, Boston, MA 02111, or Dr Young (Radiological Case of the Month), Department of Radiology, Children's Hospital of Pittsburgh, 125 DeSoto St, Pittsburgh, PA 15213. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.

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MERUVAX® (Rubella Virus Vaccine, Live, MSD)—Immunization against rubella (German measles) in children 15 months of age to puberty. May be given as early as 12 months if that offers greater convenience in scheduling. May be useful for postpubertal males to prevent or control rubella outbreaks in circumscribed population groups. In postpubertal females vaccination must not be undertaken unless the woman is not pregnant, is susceptible to rubella (as shown by Hemagglutination Inhibition test), understands it is imperative not to become pregnant for next three months and will follow a medically acceptable method for pregnancy prevention (also in immediate postpartum period), and is informed of frequent occurrence of self-limited arthralgia and possible arthritis beginning two to four weeks after vaccination.

M·M·R® (Measles, Mumps and Rubella Virus Vaccine, Live, MSD)—Simultaneous immunization against measles, mumps, and rubella in children 15 months of age to puberty.

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MUMPSVAX® (Mumps Virus Vaccine, Live, MSD)—Immunization against mumps for children 15 months of age or older and adults. May be given as early as 12 months if that offers greater convenience in scheduling.

Contraindications: Pregnancy or the possibility of pregnancy within three months following vaccination (see special considerations for ATTENUVAX below); hypersensitivity to neomycin; in patients hypersensitive to chicken or chicken eggs or feathers or, for rubella-containing vaccines, duck or duck eggs or feathers, weigh benefits of immunization against potential risks of hypersensitivity reactions; any febrile respiratory illness or other active infection; for measles-containing vaccines, active untreated tuberculosis, therapy with ACTH, corticosteroids (except as replacement therapy, e.g., for Addison's disease), irradiation, alkylating agents, or antimetabolites; blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems; primary immunodeficiency states, including cellular immune deficiencies, hypogammaglobulinemic, and dysgammaglobulinemic states.

ATTENUVAX—PREGNANCY: The effects of ATTENUVAX on fetal development are unknown at this time. Live attenuated measles virus vaccine should not be given to persons known to be pregnant; furthermore, pregnancy should be avoided for three months following vaccination. Reports have indicated that natural measles during pregnancy enhances fetal risk. Increased rates of spontaneous abortion, stillbirth, congenital defects, and prematurity have been observed subsequent to natural measles during pregnancy. There are no adequate studies of the attenuated (vaccine) strain of measles virus in pregnancy. However, it would be prudent to assume that the vaccine strain of virus is also capable of inducing adverse fetal effects for up to three months following vaccination.

Vaccine administration to post-pubertal females entails a potential for inadvertent immunization during pregnancy. Theoretical risks involved should be weighed against the risks that measles poses to the unimmunized adolescent or adult. Advisory committees reviewing this matter have recommended vaccination of post-pubertal females who are presumed to be susceptible to measles and not known to be pregnant. If a measles exposure occurs during pregnancy, one should consider the possibility of providing temporary passive immunity through the administration of immune serum globulin (human).

Precautions: Administer subcutaneously; *do not give intravenously.* Epinephrine should be available for immediate use should an anaphylactoid reaction occur. Should not be given less than one month before or after immunization with other *live* virus vaccines, with the exception of monovalent or trivalent poliovirus vaccine, live, oral, which may be administered simultaneously. Vaccinations should be deferred for at least three months following blood or plasma transfusions or administration of more than 0.02 ml human immune serum globulin per pound of body weight. Rubella vaccine may be given in the immediate postpartum period to those nonimmune women who have received anti Rh_0 (D) immune globulin (human) without interfering with vaccine effectiveness.

Attenuated measles, mumps, and rubella virus vaccines, live, given separately, may result in a temporary depression of tuberculin skin sensitivity; therefore, if a tuberculin test is to be done, it should be administered before or simultaneously with any of these virus vaccines.

Measles-Containing Vaccines—Due caution should be employed in children with a history of febrile convulsions, cerebral injury, or any other condition in which stress due to fever should be avoided. The physician should be alert to the temperature elevation which may occur 5 to 12 days after vaccination. The occurrence of thrombocytopenia and purpura has been extremely rare.

Rubella-Containing Vaccines—Excretion of live attenuated rubella virus from the throat has occurred in the majority of susceptible individuals administered rubella vaccine. There is no definitive evidence to indicate that such virus is contagious to susceptible persons who are in contact with vaccinated individuals. Consequently, transmission, while accepted as a theoretical possibility, has not been regarded as a significant risk.

Adverse Reactions: To date, clinical evaluation of the combination vaccines has revealed those adverse reactions expected to follow administration of the monovalent vaccines given separately.

Measles-Containing Vaccines—Occasionally, moderate fever (101-102.9 F); less commonly, high fever (above 103 F); rarely, febrile convulsions. Infrequently, rash, usually minimal without generalized distribution. Reactions at injection site. Local reactions characterized by marked swelling, redness, and vesiculation at the injection site of attenuated live measles virus vaccines have occurred in children who received killed measles vaccine previously; the combination vaccines were not given under this condition in clinical trials.

Experience from more than 80 million doses of all live measles vaccines given in the U.S. through 1975 indicates that significant central nervous system reactions such as encephalitis and encephalopathy, occurring within 30 days after vaccination, have been temporally associated with measles vaccine approximately once for every million doses. In no case has it been shown that reactions were actually caused by vaccine. The Center for Disease Control has pointed out that "a certain number of cases of encephalitis may be expected to occur in a large childhood population in a defined period of time even when no vaccines are administered." However, the data suggest the possibility that some of these cases may have been caused by measles vaccines. The risk of such serious neurological disorders following live measles virus vaccine administration remains far less than that for encephalitis and encephalopathy with natural measles (one per thousand reported cases). There have been reports of subacute sclerosing panencephalitis (SSPE) in children who did not have a history of natural measles but did receive measles vaccine. Some of these cases may have resulted from unrecognized measles in the first year of life or possibly from the measles vaccination. Based on estimated nationwide measles vaccine distribution, the association of SSPE cases to measles vaccination is about one case per million vaccine doses distributed, far less than the 5-10 cases of SSPE per million cases of natural measles.

Rubella-Containing Vaccines—Adverse reactions may include fever and rash; mild local reactions such as erythema, induration, tenderness, and regional lymphadenopathy; thrombocytopenia and purpura; allergic reactions such as urticaria; and arthritis, arthralgia, and polyneuritis.

Moderate fever (101-102.9 F) occurs occasionally, and high fever (103 F) occurs less commonly. Rash occurs infrequently and is usually minimal without generalized distribution. Encephalitis and other nervous system reactions have occurred very rarely.

Transient arthritis, arthralgia, and polyneuritis vary in frequency and severity with age and sex, being greatest in adult females and least in prepubertal children. Symptoms relating to joints (pain, swelling, stiffness, etc.) and to peripheral nerves (pain, numbness, tingling, etc.) occurring within approximately two months after vaccination should be considered as possibly vaccine related. These symptoms need not be associated with other features of rubella, such as fever, rash, and lymphadenopathy. In prepubertal children, the symptoms have generally been mild and of no more than three days' duration, with an incidence of less than 1 percent for reactions that would interfere with normal activity or necessitate medical attention. In teen-age girls, the rates of reactions are somewhat higher but probably do not exceed 5 to 10 percent. In women, the rates are greater and may exceed 30 percent; the symptoms in older females tend to be more prominent and of longer duration, rarely persisting for a matter of months, but have not generally interfered with normal activity. There is, at present, no evidence that the joint involvement or neuritis accompanying infection with either natural rubella or the attenuated viruses predisposes to any of the known chronic arthritic or neurologic diseases. Transient arthralgia and arthritis in nonimmune males may occur; however, as in the natural disease, the incidence is expected to be lower than in women.

Mumps-Containing Vaccines—Parotitis. Rarely, purpura and allergic reactions such as urticaria. Very rarely, encephalitis and other nervous system reactions. With the monovalent mumps vaccine, mild fever occurs occasionally, and fever above 103 F is uncommon.

Shipment, Storage, and Reconstitution: During shipment, to insure that there is no loss of potency, the vaccine must be maintained at a temperature of 10 C (50 F) or less. Before reconstitution, store vaccines at 2-8 C (35.6-46.4 F) and *protect from light.* Use only diluent supplied to reconstitute vaccines. If not used immediately, store reconstituted vaccines in a dark place at 2-8 C (35.6-46.4 F), and discard if not used within eight hours.

Color change: The usual color of the vaccine when reconstituted is pinkish to red due to the presence of phenol red, a pH indicator. Some vaccine which has been shipped in dry ice may exhibit a variation in color when reconstituted because carbon dioxide has been absorbed from the dry ice. This vaccine, if crystal clear on reconstitution, is acceptable for use whether it is red, pink, or yellow.

How Supplied: *ATTENUVAX® (Measles Virus Vaccine, Live, Attenuated, MSD)*—Single-dose vials of lyophilized vaccine, containing when reconstituted not less than 1,000 $TCID_{50}$ (tissue culture infectious doses) of measles virus vaccine expressed in terms of the assigned titer of the FDA Reference Measles Virus, and approximately 25 mcg neomycin.

BIAVAX® (Rubella and Mumps Virus Vaccine, Live, MSD)—Single-dose vials of lyophilized vaccine, containing when reconstituted not less than 1,000 $TCID_{50}$ of rubella virus vaccine, live, and 5,000 $TCID_{50}$ of mumps virus vaccine, live, expressed in terms of the assigned titer of the FDA Reference Rubella and Mumps Viruses, and approximately 25 mcg neomycin.

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Each of these vaccines is supplied as a single-dose vial packed with a disposable syringe containing diluent and fitted with a 25-gauge, 5/8" needle, and as a box of 10 single-dose vials with an accompanying box of 10 diluent-containing disposable syringes with affixed needles.

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Saddle Embolus Occluding Pulmonary Arteries

Parenteral alimentation is invaluable in salvaging infants who otherwise would have been unable to survive congenital anomalies of the intestine or necrotizing enterocolitis.[1]

A catastrophe complicated an infant's recovery from bowel resection and intolerance to oral feeding.

Report of a Case.—A 14-day-old, full-term baby girl was referred with bloody stools and abdominal distention; roentgenograms demonstrated pneumatosis intestinalis and air in the portal venous system. Nine centimeters of necrotic ileum, cecum, and ascending colon were removed, and total parenteral nutrition given via superior vena caval catheters placed first in each external jugular vein and finally in the left internal jugular vein. Her nutritional status greatly improved, but even 5% glucose per ostium was intolerable. At 2 months of age, pallor and orthopnea with slow gasping respirations suddenly developed; she died half an hour later. Clinical impression was pulmonary embolus.

Autopsy showed a small, fairly well-nourished infant weighing 3,490 g, with healed ileostomy and laparotomy scars and fine adhesions between loops of small and large bowel. A hard rubbery mass completely filling the main pulmonary trunk proved to be an embolus 2.6 cm long extending from the crista supraventricularis of the right ventricle through the pulmonary valve then extending 0.6 cm into the right and left pulmonary arteries—a true "saddle embolus" (Fig 1). It had dislodged from a thrombus adherent to the medial surface of the superior vena cava that was lined with gray friable granulation tissue from its junction with the innominate vein to the right atrium (Fig 2). The intima of the medial side of the superior vena cava had been destroyed; a portion of the trabeculae carnae beneath the thrombus in the right atrium was necrotic.



Fig 1.—Saddle embolus lodged in main pulmonary trunk extending into right and left pulmonary arteries completely occluding flow of blood.



Fig 2.—Friable granulation tissue adherent to medial wall of superior vena cava extending into right atrium.

Comment.—The complications of total parenteral nutrition of . . . "thrombosis, embolism, bacterial and fungal infections, hyperammonemia, metabolic acidosis, hyperglycemia, rebound hypoglycemia, glycosuria and osmotic diuresis . . . "[2] have been reported. Our case of pulmonary embolism plus one report by Firor,[3] three in a series of 200 infants by Ryan et al,[4] and eight by Muller[5] from Germany bring the total reports in infants to 13. Since there is no warning of impending pulmonary embolus, the only means of prevention is to limit the use of total parenteral nutrition to as short a time as possible.

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Congenital Hypopituitarism and Conjugated Hyperbilirubinemia in Two Infants

Congenital hypopituitarism in children is a well-recognized entity.[1-10] The association of severe neonatal hypoglycemia with growth hormone or adrenocorticotropin insufficiency and with the presence of a microphallus and cryptorchidism in some of the male patients is well established.[6-8] Hepatomegaly and jaundice have been found in some of these patients.[8,9] However, the association of hypopituitarism with conjugated hyperbilirubinemia has been previously documented in only one report.[10]

We have recently encountered two infants with hypopituitarism and hypoglycemia, both of whom also had an increased direct serum bilirubin level.

Report of Cases.—CASE 1.—This patient was born after 45 weeks' gestation to a 23-year-old para 0 woman by cesarean section for cephalopelvic disproportion. Apgar scores were 3 and 5 at one and five minutes, respectively, for which the infant required oxygen. Physical examination showed a 4.6-kg male infant, 53 cm in length, with polydactyly and microphallus. Stretched length of the phallus was 2.0 cm; both testes were palpable in the scrotum. Liver was felt 1 cm below the right costal margin and spleen tip was palpable; neurological examination was unremarkable. The immediate neonatal period was complicated by asymptomatic hypoglycemia (blood glucose level, 8 mg/dl) that was easily controlled with an intravenous infusion of 20% dextrose and water, and later with frequent feedings. Laboratory findings for complete blood cell (CBC) count and urinalysis (with a normal specific gravity) were normal. Roentgenographic examination of the skull and kidneys showed no abnormality. During two episodes of spontaneous hypoglycemia, blood glucose concentrations were 32 mg/dl and 19 mg/dl, the plasma growth hormone levels were 1.9 ng/ml and 1.5 ng/ml, and the serum cortisol levels were 2.8 μg/dl and 4.7 μg/dl.

Serum thyroxine level was 5.7 μg/dl and thyroid-stimulating hormone was less than 3.8 μU/ml at 4 weeks of age. At that same time, serum luteinizing hormone level was 33 ng/ml (normal range at 1 to 24 months, 10 to 40 ng/ml), follicle-stimulating hormone level was 13 ng/ml (normal range at 1 to 24 months, 40 to 200 ng/ml), and testosterone level was 25 ng/dl (normal range at 1 to 4 months, 50 to 340 ng/dl). Urinary 17-ketosteroids were 0.15 mg/24 hr (normal, <0.5 mg/24 hr), and urinary 17-hydroxycorticosteroids were 0.18 mg/sq m/24 hr (normal, 3 ± 1 mg/sq m/24 hr). A diagnosis of hypopituitarism was made.

The infant became jaundiced on day 2. Jaundice persisted, peaking at 18 days of age at a total serum bilirubin level of 14.6 mg/dl, with a direct-reacting fraction of 5.3 mg/dl. The SGOT level was 42 IU/liter; SGPT level, 6 IU/liter; alkaline phosphatase level, 85 mIU/liter; prothrombin time, 11.5 seconds. Tests for hepatitis B surface antigen, toxoplasmosis, rubella, cytomegalovirus and herpes simplex titers, and urine for cytomegalovirus were negative; α_1 antitrypsin was normal. A cholestyramine augmented rose bengal sodium I 131 test at 6 weeks of age showed 17% excretion of dye in stools over a 72-hour period. An open liver biopsy specimen showed noticeable intralobular bile stasis and centrilobular giant cell transformation that were compatible with neonatal hepatitis.

The patient was started on a regimen of growth hormone 1 unit intramuscularly (IM) every other day; cortisone acetate, 15 mg IM every three days; and levothyroxine sodium, 0.05 mg orally every day at 4 weeks of age. Two months after treatment was started, the patient's height and weight were at the tenth percentile. He has had no further episodes of hypoglycemia and his total serum bilirubin level was 0.3 mg/dl.

CASE 2.—This patient is a 2.9-kg female infant, born to a 26-year-old para 1 class D diabetic mother after 33 weeks' gestation. This child had a stormy neonatal period, having hypoglycemia, hypocalcemia, and severe respiratory distress syndrome develop in the first days of life. Indirect hyperbilirubinemia secondary to ABO incompatibility required an exchange transfusion on the third day of life. She was discharged at 3½ weeks of age.

At 9 weeks of age, she was transferred to the Johns Hopkins Hospital, Baltimore, after a respiratory arrest and an episode of severe hypoglycemia. Physical examination showed a small, jaundiced infant 53 cm in length, 3,580 g in weight, in whom a firm liver and spleen were felt 3 cm below the right costal margin and 4 cm below the left costal margin, respectively. Spontaneous hypoglycemia occurred on several occasions during the next two days, with blood glucose values as low as 16 mg/dl after a two-hour fast.

Laboratory data included normal CBC and urinalysis (with a normal specific gravity). A three-hour glucagon stimulation test[11] showed very low plasma cortisol values (1.9 μg/dl at 0 minutes, 1.7 μg/dl at 60 minutes, and 2.5 μg/dl at 120 minutes) and growth hormone levels (<0.8 ng/ml at 0, 60, and 120 minutes); glucose concentrations went from 26 mg/dl at 0 minutes to 41 mg/dl at 30 minutes, 16 mg/dl at 90 minutes, and 18 mg/dl at 120 minutes during this test. Serum thyroxine level was 4.6 μg/dl and thyroid-stimulating hormone was 4.3 μU/ml. Total serum bilirubin level was 7.5 mg/dl; direct bilirubin level, 4.5 mg/dl; SGOT level, 130 IU/liter; SGPT level, 36 IU/liter; alkaline phosphatase level, 385 mIU/liter; and prothrombin time, 10.5 seconds. Tests for hepatitis B surface antigen and toxoplasmosis, rubella, cytomegalovirus and herpes simplex titers were negative; α_1 antitrypsin and ceruloplasmin levels were normal. Liver biopsy specimen, taken six days after glucocorticoid therapy was begun showed minimal inflammatory changes.

Because of poorly controlled hypoglycemia even with frequent feedings and intravenous dextrose infusions, the patient was started on a regimen of hydrocortisone 15 mg three times a day. No further hypoglycemic episodes occurred; liver and spleen decreased substantially in size. Serum bilirubin level decreased to 4.5 mg/dl, total, 2.5 mg/dl, direct, by the third day of treatment. Cortisone acetate was reduced to replacement dosage, 10 mg IM every three days; treatment with levothyroxine sodium, 0.025 mg orally every day, and growth hormone, 1 unit IM every other day, was begun. One week later, the liver edge was palpable 1 cm below the right costal margin, the spleen was firm and felt 1.5 cm below the left costal margin. Serum thyroxine level was 8.2 μg/dl and glucose values ranged between 45 and 90 mg/dl. Four weeks after discharge, glucose level was 90 mg/dl, total serum bilirubin level, 1.1 mg/dl; and direct bilirubin level, 0.6 mg/dl.

Comment.—These two patients had severe neonatal hypoglycemia, inadequate plasma growth hormone and cortisol response to hypoglycemia and glucagon stimulation, and low levels of thyroid-stimulating hormone and thyroxine. In addition, the male patient had a microphallus. The hypoglycemia was corrected in both infants by glucocorticoid and growth hormone therapy. These criteria establish the diagnosis of hypopituitarism.[6-8]

The hepatomegaly together with increased serum total and direct bilirubin concentrations and increased levels of SGOT were unexpected. Since direct hyperbilirubinemia has been previously reported only once in patients with hypopituitarism,[10] it was of interest to try to determine if there was a direct relationship between hypopituitarism and liver disease. There was no laboratory evidence of any infectious or infiltrative systemic disease that could explain damage to the pituitary gland, liver, and spleen, either in utero or early in the neonatal period, nor were the liver biopsy specimens helpful in this regard.

This article reports the association of hypopituitarism, hepatomegaly, and direct hyperbilirubinemia in two infants. Assessment of more patients, however, will be necessary to determine if this relationship has causal, diagnostic, or therapeutic importance. In the meantime, perhaps hypopituitarism should be included in the differential diagnosis of direct hyperbilirubinemia.

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Rocky Mountain Spotted Fever in an Infant: Diagnosis in Siblings

The incidence of Rocky Mountain spotted fever (RMSF) in the United States has been increasing over the past 15 years.[1] This disease had noticeable seasonal and geographic predilection, being most prevalent in the spring and summer and in the southeastern United States.[1] About 70% of the cases occur in children 3 to 15 years of age.[2] The purpose of this report is to describe two siblings with the disease, which was diagnosed in an nonendemic area, Wisconsin. The younger sibling, a 6-month-old, contracted the disease in infancy, an event infrequently recorded but apparently associated with marked morbidity and mortality.[3-5]

Report of Cases.—CASE 1.—In May 1977, this 6-month-old male infant visited relatives in northern Mississippi. Twelve days before admission, fever and a generalized maculopapular rash developed. He was exposed to a neighbor's dog known to have ticks, but had no known tick bites. He slept with his 3-year-old brother (case 2). Five days before admission he was seen by a physician in Mississippi who prescribed oral ampicillin trihydrate. Fever and rash persisted and the infant vomited and became lethargic. The family returned to Milwaukee and he was admitted to Milwaukee Children's Hospital.

Results of physical examination revealed an acutely ill-appearing infant with a shrill cry and moderate nuchal rigidity. His temperature was 40 °C. Nonpitting edema of the hands, feet, and periorbital regions was noted. An erythematous maculopapular rash was distributed over the entire body, most prominently on the face and extremities, including the palms and soles. A purpuric 2 × 2-cm skin lesion was subsequently noted over the right lateral malleolus. White blood cell count was 20,000/cu mm, with 30% bands and 28% polymorphonuclear leukocytes. Hemoglobin level was 9.2 g/dl. Platelet count was 84,000/cu mm. The prothrombin time was 15.5 seconds (control, 12.0 seconds) and the partial thromboplastin time was 51.5 seconds (control, 36.5 seconds). Fibrinogen level was 110 mg/dl. Erythrocyte sedimentation rate was 4 mm/hr. Cerebrospinal fluid from a lumbar puncture had 37 WBC/cu mm (100% mononuclears), a glucose level of 61 mg/dl, and a protein level of 70 mg/dl. A chest roentgenogram was normal. Cerebrospinal fluid, blood, urine, and throat cultures for bacterial and viral pathogens showed no growth. A *Proteus* OX-19 titer obtained on admission was negative. A RMSF complement fixation titer was < 1:8.

Intravenous (IV) therapy with ampicillin sodium (200 mg/kg/day) and chloramphenicol (100 mg/kg/day) was begun. After two days, ampicillin therapy was discontinued. The patient received ten days of chloramphenicol therapy (five days IV). His fever slowly returned to normal over a one-week period. The platelet count dropped to 50,000/cu mm on day 4, but rose to 128,000/cu mm by the ninth hospital day. The prothrombin time and partial thromboplastin time returned to normal levels after one week of hospitalization. He was discharged on the tenth hospital day. One month after disease onset, a *Proteus* OX-19 titer was negative but the RMSF complement fixation titer was positive at 1:16. A final RMSF titer drawn ten weeks after the disease onset was 1:64.

CASE 2.—The 3-year-old brother of case 1 had a course similar to, but milder than his sibling's. High fever and maculopapular rash localized to the wrists and ankles developed. This child was known to play in the weeds around the house, but had no known tick bites. He received several days therapy with oral ampicillin trihydrate while in Mississippi. On admission to Milwaukee Children's Hospital, he had a temperature of 39.6 °C. There were no meningeal signs, but periorbital edema and nonpitting edema of the hands and feet were present. Petechial lesions were noted on the wrists and abdomen. All cultures were negative. Cerebrospinal fluid from a lumbar puncture showed 1,451 RBC/cu mm and 46 WBC/cu mm, with 70% polymorphonuclear leukocytes and 30% mononuclear cells. The CSF glucose level was 53 mg/dl and the protein level was 42 mg/dl. His peripheral WBC count was 16,700/cu mm, with 20% bands and 54% polymorphonuclear leukocytes. Platelet counts were 531,000/cu mm and subsequently rose to 880,000/cu mm on the sixth hospital day. On admission, his prothrombin time was 13.0 seconds (control, 12.0 seconds) and the partial prothrombin time was 43 seconds (control, 38.5 seconds). Fibrinogen level was 360 mg/dl. Erythrocyte sedimentation rate was 76 mm/hr. A *Proteus* OX-19 titer was positive at 1:5,120. A RMSF complement fixation titer was positive at a dilution of 1:1,024. Intravenous ampicillin sodium (200 mg/kg/day) and chloramphenicol (100 mg/kg/day) were administered for two days, then oral chloramphenicol therapy (75 mg/kg/day) was continued alone for a total of ten days. The child defervesced after five days and was discharged on the tenth hospital day.

Comment.—To our knowledge, case 1 is apparently the youngest serologically confirmed case of RMSF reported in the literature. A clinically diagnosed case of congenital RMSF was reported in 1904.[5] Only two other infants, 9 and 10 months of age, with RMSF have been described.[3,4] At least two of these infants died. The infant was clearly the more critically ill of our patients as seen by his high temperature marked toxic condition, purpuric skin lesion, and evidence of consumptive coagulopathy.

The apparent increased severity of RMSF in infancy could relate to a relatively weak or delayed immune response to this infection in the young child. Poor complement fixation antibody response in older patients with confirmed RMSF has been correlated with poor production of IgG immunoglobulin.[6] A positive *Proteus* OX-19 titer never developed in our infant patient, whereas the older one had high levels of *Proteus* agglutinins. Complement fixing antibodies specific for RMSF did not develop in the younger child until four weeks after disease onset, and these were of low level (1:16). The older child had very high antibody levels (1:1,064) early in the course of infection. Of the three previously reported cases of RMSF in infancy, in only one was a Weil-Felix test performed and that was negative.[4] In none were RMSF complement fixation titers performed.

The history of a tick bite can be elicited in 60% of the cases of RMSF.[1] Although our older patient presumably acquired his infection from a tick bite, the mechanism by which the infant sibling became infected is unknown. An infected tick could have been transferred during sleep from the older to the younger child. Cases of RMSF in siblings, although unusual, have been reported previously.[7] Since the incidence of infected ticks in endemic areas is only about 5%, it seems likely that both children were bitten by the same tick.[8] Transmission of RMSF through the respiratory tract, a known hazard to laboratory workers, seems unlikely.[9]

Rocky Mountain spotted fever is rarely fatal in children if diagnosed and treated, but mortality may reach 25% when it is not recognized.[10] Before

the diagnosis of RMSF in these brothers, there had not been a reported case of RMSF in Wisconsin for at least 15 years.[1] In today's mobile society, in which rapid movement of individuals is the rule, patients with infectious diseases nonendemic for given areas require prompt recognition of their infections for effective and potentially life-saving therapy.

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Dr Leonard Gorenstein allowed us to describe this patient. Rocky Mountain spotted fever titers were performed by the Virology Department, Bureau of Laboratories, Milwaukee Health Department.

Nonproprietary Names and Trademarks of Drugs

Ampicillin sodium—*Alpen-N, Amcill-S, Omnipen-N, Penbritin-S for injection, Polycillin-N for injection, Principen-N.*
Ampicillin trihydrate—*Amcill, Alpen, Polycillin, Principen.*

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Klippel-Feil Malformation Complex in Fetal Alcohol Syndrome

The fetal alcohol syndrome (FAS) consists of intrauterine growth retardation, microcephaly, short palpebral fissures, maxillary hypoplasia, various limb and joint anomalies, cardiac defect, and variable degrees of mental deficiency.[1,2] Vertebral and rib abnormalities have only been reported in two previous cases.[3] We now describe two more children with the Klippel-Feil malformation complex in the fetal alcohol syndrome.

Report of Cases.—CASE 1.—A 4-year-old boy was referred to the University of Oregon Crippled Children's Division, Eugene, for evaluation of multiple dysmorphic features and short stature. His mother, aged 30 years, had an excessive ethanol intake daily during the first six months of pregnancy but decreased her alcohol consumption during the third trimester. Two previously nonalcoholic pregnancies had resulted in normal offspring. The patient was born at term, but weighed only 1.82 kg. An inguinal hernia was repaired at age 14 months.

At age 4 years 5 months, his height was 82 cm, weight was 10.2 kg, head circumference was 47.6 cm, and bone age was 2 years. He had short palpebral fissures, bilateral medial epicanthal folds, and maxillary hypoplasia. His neck was short and broad with a low posterior hairline and limited range of movement with a left torticollis (Fig 1). The right shoulder and scapula were higher than the left. He had limitation of supination of the right forearm, bilateral fifth finger clinodactyly, and an unusual bridged palmar creased pattern of his right hand. Intellectual development was not substantially delayed. Cervical spine roentgenograms and tomograms confirmed multiple rib deformities, occipitalization of the first cervical vertebra, and multiple vertebral defects, including a hemivertebra at the first thoracic level (Fig 2).

CASE 2.—A 16-year-old boy was evaluated by one of us (D.W.S.) at Letterman Army Hospital, San Francisco. The boy's mother was a severe alcoholic during his pregnancy. An older brother was born before the mother became alcoholic and he was of normal stature and intelligence. The

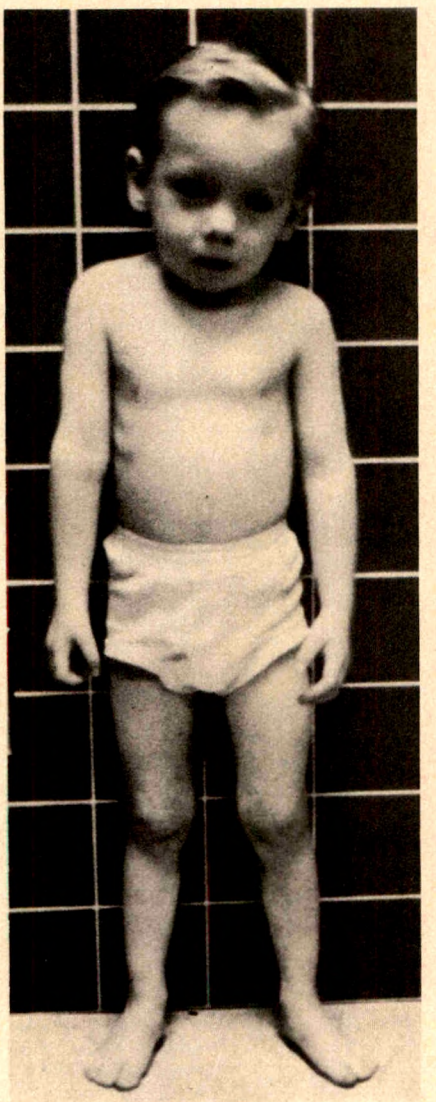


Fig 1.—Case 1. Frontal view.

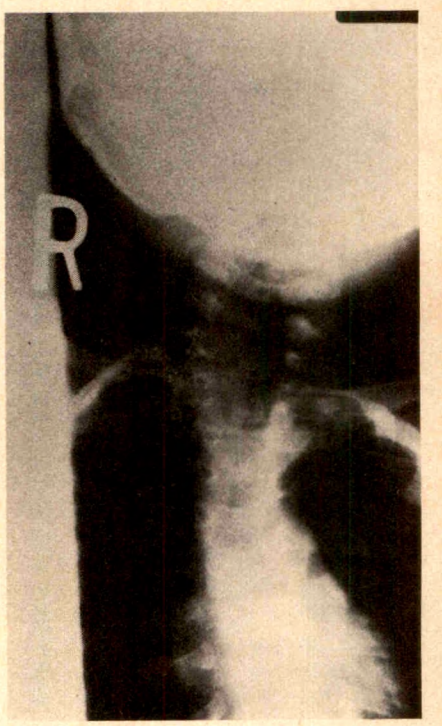


Fig 2.—Case 1. Chest and neck film with multiple vertebral and rib deformities.

patient weighed only 1.4 kg after a full-term gestation. At age 16 years, his height was 155 cm, weight was 40 kg, and head circumference was 50.6 cm. The facies had asymmetrical ocular ptosis, relatively short nose, poorly defined philtrum, relatively thin upper lip, and short palpebral fissures. The third fingers had mild bilateral camptodactyly. Intelligence quotient was 70. He had a short neck with limited mobility, low hairline, and mild lateral webbing. Roentgenograms showed multiple cervical vertebral defects, including hemivertebrae. A unilateral radioulnar synostosis was also noted.

Comment.—The Klippel-Feil malformation complex was originally defined in 1912 as the triad of short neck, low posterior hairline, and painless limitation of cervical movement.[4] Roentgenographic studies have demonstrated various anomalies of the cervical vertebrae and a high association with rib deformities. More recently, those patients have been found to have an increased incidence of anomalies involving the genitourinary, cardiac, auditory, and central nervous systems.[5]

The association of rib and craniovertebral anomalies with chronic ethanol exposure during gestation was reported by Chernoff[6] from studies with mice. Our report documents a similar association in humans, and hence confirms the report by Lowrey[3]; Dr K. L. Jones at the University of California at San Diego (Dr Jones, oral communication, July 1977) has also seen such a patient.

Robinson[7] recently reviewed various hypotheses regarding the teratogenic factors involved. Is it due to a primary effect of ethanol or its metabolites on developing tissues, or does alcohol work in concert with nutritional or other environmental/genetic factors? Chernoff's mouse model provided evidence of a direct teratogenic effect for ethanol or its metabolites. This work used chronic ethanol exposure with provision for adequate amounts of dietary nutrients and vitamins. A prospective, collaborative study reported by Ouellette et al[8] and Rosett et al[9] presents evidence for a primary teratogenic effect. This work demonstrated twice the incidence of birth defects with heavy alcohol use compared with mild or moderate use in pregnant women. Nutritional intake, drug use, and sociologic factors were not substantially different among the women in different alcohol-intake groups. Women who reduced their alcohol consumption during pregnancy had a reduced incidence of birth defects and growth abnormalities in their children.

Different species are noted to have different congenital defects with embryologic exposure to ethanol.[6,7] The finding of the Klippel-Feil malformation complex as one feature in several patients with the fetal alcohol syndrome suggests that this is a nonrandom occurrence in humans. The potentiality of vertebral anomalies should be considered in any infant born of a woman with a history of heavy alcohol intake during pregnancy.

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Mouthwash-Induced Hypoglycemia

Acute ethyl alcohol ingestion is an uncommon but well-documented cause of hypoglycemia in infancy and childhood.[1] We wish to report two cases of ethanol-induced hypoglycemia seen on our pediatric service in a five-month period. Both were caused by the ingestion of Scope, a mint-flavored mouthwash with a 16% ethyl alcohol content.

Report of Cases.—CASE 1.—A 3-year-old boy was noted to be ataxic and less active than usual by his parents before breakfast on the morning of admission. The child had last eaten the previous evening and had slept the entire night without incident. He had an episode of generalized tonic-clonic movements of his extremities lasting approximately two minutes. He was rushed to the emergency room where he was found to be arousable, but kept lapsing into periods of unconsciousness. History showed that the mother had found a nearly empty 720-ml (24-oz) bottle of Scope mouthwash (which had been full the previous day) in the bathroom. Scope ingestion was suspected and later was confirmed, but we were unable to determine a time of ingestion. According to the mother, there was no other readily available source of alcohol to the child.

Examination of the patient showed he had a temperature of 36.6 °C, a pulse rate of 120 beats per minute and regular, a respiration rate of 24/min, a blood pressure of 85/45 mm Hg, a height of 91 cm (fifth percentile), and a weight of 12 kg (third percentile). The rest of the findings on the physical examination except for the patient's level of consciousness were normal.

The serum glucose level was 17 mg/dl; the sodium level, 133 mEq/liter; the potassium level, 3.6 mEq/liter; the chloride level, 97 mEq/liter; the CO_2 content, 10 mEq/liter; and the serum ethanol level, 30 mg/dl (greater than 150 mg/dl is considered legally intoxicated).

An intravenous (IV) infusion of 50 ml of 25% glucose in water (4 ml/kg) was given rapidly followed by continuous infusion of 10% dextrose in water at the rate of 8 mg/kg/min. About 20 to 30 minutes later, the child was completely responsive and awake. Two hours after admission, the blood glucose level was 247 mg/dl; the sodium level, 144 mEq/liter; the potassium level, 4.8 mEq/liter; the chloride level, 106 mEq/liter; and the CO_2 content, 16.2 mEq/liter. He continued to do well and was started on oral feeding. The IV solution was changed to 5% dextrose in hypotonic saline and was discontinued later. He was discharged home the next day.

CASE 2.—A 4-year-old girl was found unconscious on the bathroom floor at 9 AM on the morning of admission. She had last eaten the previous evening. The mother thought the child was sleeping and put her back in bed, but became concerned at 1 PM when the child could not be aroused. She was brought to the emergency room where no history of ingestion of toxic substances was immediately available. Her temperature was 36.9 °C; pulse rate, 72 beats per minute and regular; respiratory rate, 14/min; blood pressure, 90/50 mm Hg; height,

108 cm (90th percentile); and weight, 19 kg (92nd percentile); she was responsive only to painful stimuli. The rest of the findings on physical examination were normal. A nasogastric tube was inserted and approximately 60 ml of fluid with a minty odor was returned. A presumptive diagnosis of mouthwash ingestion and poisoning was made, and this was confirmed later after talking to the patient. According to the mother, there was no other readily available source of alcohol at home.

The serum glucose level was 14 mg/dl; the sodium level, 137 mEq/liter; the potassium level, 2.1 mEq/liter; the chloride level, 100 mEq/liter; the CO_2 content, 10.2 mEq/liter; and the serum ethanol level, 20 mg/dl. An IV infusion of 10 ml of 50% glucose was given over five minutes followed by continued infusion of 5% dextrose in hypotonic saline at the rate of 60 ml/hr. Potassium chloride was added to the infusion at the rate of 20 mEq/liter. The patient was awake, alert, and fully responsive 15 minutes after therapy was initiated. Three hours after admission the blood glucose level was 207 mg/dl; the sodium level, 134 mEq/liter; the potassium level, 3.7 mEq/liter; the chloride level, 107 mEq/liter; and the CO_2 content, 16 mEq/liter. She was given oral feedings, and the IV infusion was gradually discontinued after six hours. The patient did well subsequently and was discharged home the next day.

Comment.—Our two cases were successfully treated children, but the literature does contain reports of fatalities with alcohol-induced hypoglycemia in children.[2,3] It is important to recognize that in a child, unlike an adult, poor nutritional status or a prolonged fast before alcohol ingestion is not necessary for hypoglycemia to occur. In one report, eight of nine children with alcohol-induced hypoglycemia were well nourished.[4] In addition, one should be aware that alcohol-induced hypoglycemia is thought not to be dose related.[5]

Since accidental poisoning is one of the major causes of death in pediatrics, those involved in the primary care of children should be acutely aware of poisoning as a possibility in any child who comes to them in coma. Our purpose is to emphasize that short-term ethanol ingestion, whether in beverage form or as a component of some other liquid such as mouthwash or cough medicine (eg, Terpin Hydrate: ethanol content, 35%; Pertussin R: ethanol content, 25%) can be potentially lethal through the induction of hypoglycemia.

Prompt recognition and treatment with IV glucose can be lifesaving in the acute case. If confronted with the management of a child who has ingested ethyl alcohol, one should assume that hypoglycemia is inevitable; therefore, such a child should have his stomach lavaged and be admitted to the hospital for monitoring of blood glucose levels. If the child is symptomatic, prompt and rapid IV administration of 1 to 2 ml/kg of 25% to 50% glucose solution is recommended, followed by continued infusion of 10% dextrose at the rate of 6 to 8 mg/kg/min until blood glucose levels are stabilized. Then, both the rate and concentration of glucose may be slowly reduced and finally discontinued once the oral feeding has been started and well tolerated. Glucose drinks may also be given prophylactically to avert hypoglycemia. Parental education about potential poisons is of equal importance as a preventative measure.

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Richard D. Baltz, MD, chairman, Department of Pediatrics, and the pediatric staff gave permission for the printing of this report.

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Meningococcal Hydrocephalus

Atypical presentations of meningococcal meningitis include acute cerebellar ataxia,[1] psychosis,[2] and hydrocephalus.[3-10] This last presentation was recognized in the past but has not been reported in the last 30 years.

Report of a Case.—A 6-month-old girl had been well, having had a normal birth and neonatal and developmental history until six weeks prior to admission to Children's Memorial Hospital, Chicago. At that time, she had a febrile illness and completed a full ten-day course of oral penicillin therapy after a throat culture was found to be positive for group A β-hemolytic streptococci. Subsequently, her mother noted that she had trouble swallowing solids, frequently gagged, had a sharp decrease in spontaneous vocalization, and lost the ability to sit without assistance. One week after the last dose of penicillin, she had a brief febrile illness without localizing signs. An examination by her pediatrician was unremarkable, and the illness resolved without therapy. The week prior to admission, she had arching of the back but fed well and remained afebrile. On the day before admission, she had several episodes of nonbilious vomiting without diarrhea or fever.

On the day of admission, she was noted to have a "sunset sign" and questionable opisthotonus. Admission examination showed a temperature of 37 °C rectally, a pulse rate of 184 beats per minute, a respiratory rate of 32, and a blood pressure of 110/78 mm Hg. She was irritable and opisthotonic, and had a bulging anterior fontanelle, bilateral papilledema, and eyes showing a sunset sign. Her right eye deviated inferolaterally. Her neck was stiff without Kernig or Brudzinski signs. Her lower extremities were hypertonic in comparison to the upper. The remainder of the examination was unremarkable, and her presumptive diagnosis was acute hydrocephalus. Admission laboratory studies gave the following values: WBC, 17,800/cu mm, hemoglobin, 12.1 g/dl, with a differential cell count of 78 polymorphonuclear leukocytes, two eosinophils, 16 lymphocytes, and seven monocytes. A left femoral angiogram on Jan 15, 1977, (Figure) showed symmetrical hydrocephalus under tension. A right ventriculoperitoneal shunt was inserted and clear ventricular fluid under high pressure was obtained. Protein content was 300 mg/dl, glucose level was 21 mg/dl, RBC count was 177/cu mm, and WBC count was 193/cu mm, with 82% mononuclear leukocytes, 18% polynuclear leukocytes; Gram stain was negative. Postoperatively, she remained afebrile, irritable, and opisthotonic. Twenty-four hours later, *Neisseria meningitidis* group B grew from culture of her ventricular fluid, and penicillin G potassium therapy, 600,000 units/kg/day, in divided doses was begun. Within 24 hours after the start of penicillin therapy, she was more alert. The child completed 14 days of penicillin therapy on Jan 29, 1977. A repeated angiogram was normal, so the ventriculoperitoneal shunt was removed. Cerebrospinal fluid obtained at that time had 9,472/cu mm of RBCs, 341/cu mm of WBCs, with 89% mononuclear leukocytes, 11% polynuclear leukocytes; glucose level was 41 mg/dl, protein level was 150 mg/dl, and Gram stain and culture were negative. The patient remained afebrile, and one week later, she was discharged with progressive neurologic improvement.

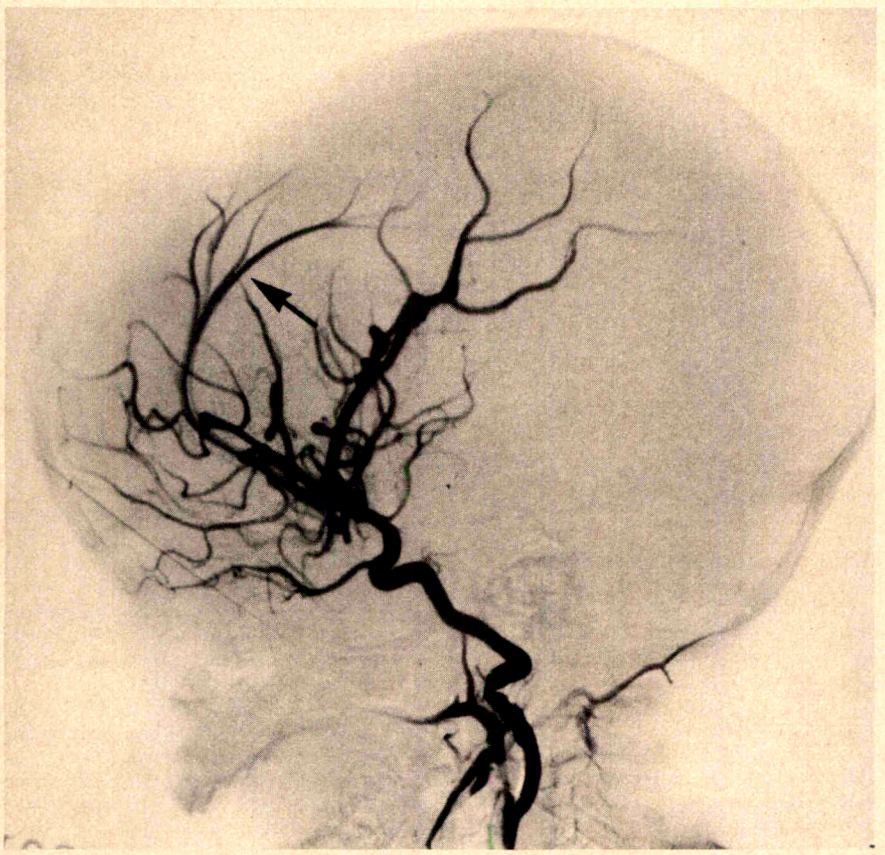
Comment.—Holt[3] in 1911, reporting 21 cases of meningococcal meningitis, described two infants who showed a slowly progressive hydrocephalus. One of the two children received Flexner's serums. Both showed nonsurgical resolution of the hydrocephalus. In 1916, Koplick[4] described the presentation of meningitis in an infant of approximately 6 weeks of age as being insidious with ongoing infection for days or weeks by the time purulent lumbar puncture fluid was obtained. In 1917, White[5] and Miller[6] described similar infants with deteriorating neurologic status, variable fever, and convulsions. Lumbar punctures were dry or sterile. The meningococcus was eventually recovered from ventricular taps done, respectively, in the fifth and sixth week of illness.

In 1921, Root[7] reviewed all previously reported cases of meningococcal meningitis in infants and reported a single case with protracted course and hydrocephalus. Although he found only one case of meningococcal meningitis with obstructive hydrocephalus during the acute stage of the disease, other chronic cases with sterile lumbar puncture and *N meningitidis* culture-positive ventricular fluid suggest that the incidence of hydrocephalus was higher. Neal et al[8] in 1926, reviewed 654 cases of meningococcal meningitis. In the first year of life, the onset was less sudden, bacteremia was usually transient, meningeal signs and fever were sometimes absent, and several weeks could elapse before the physician focused on the CNS. In these patients, loculation at the base of the brain with dry lumbar punctures was the rule.

In 1939, Silverthorne et al[9] reviewed 51 cases of meningococcal meningitis. Of these, 12 were autopsied, nine with hydrocephalus and three with basilar meningitis. The authors believed that hydrocephalus was the most common late complication in younger patients, and in their series was uniformly fatal. In 1948, Banks[10] reviewed 706 cases of meningococcal disease from 1939 to 1947. Six infants and four adults had evidence of chronic meningococcal meningitis for weeks before diagnosis and treatment. He concluded that exudate, formed in the acute phase, collected at the base of the brain and organized to give subarachnoid block. Seizures and signs of nerve root compression were present on physical examination; lumbar puncture was dry or yielded xanthochromic fluid with high protein. A few of his patients resolved the exudate and the hydrocephalus spontaneously subsided.

The case presented here strongly resembles some of the cases of meningococcal meningitis with hydrocephalus and insidious afebrile neurologic deterioration reported in the preantibiotic era. It does not resemble cases reported in the reviews of partially treated meningitis.[11,12] This report serves as a reminder of the protean manifestations of meningococcal meningitis.

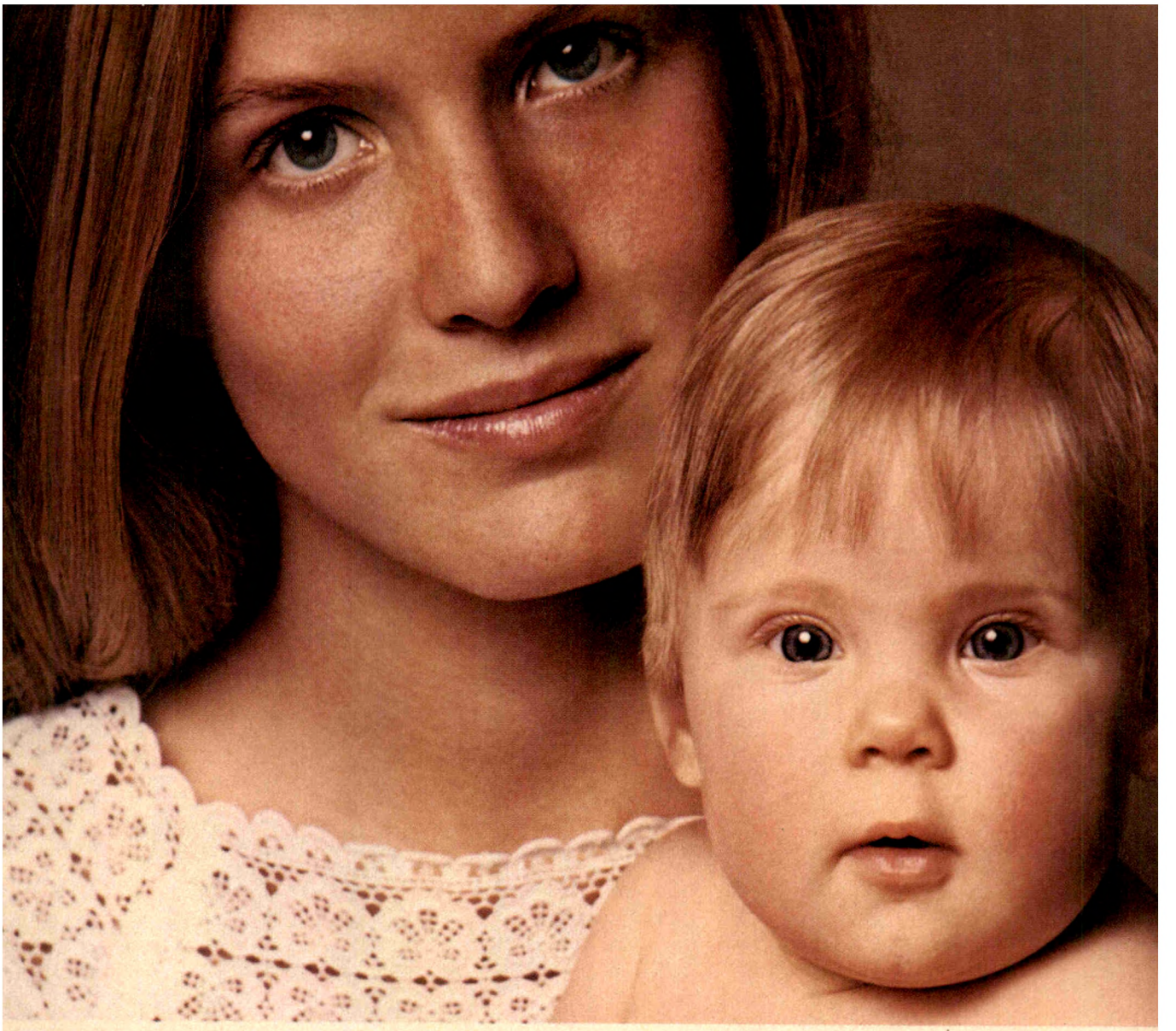
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Anterior cerebral artery under tension (arrow).

Presented at the annual residents' competition meeting of the Chicago Society of Pediatrics, Children's Memorial Hospital, Chicago, April 19, 1977.

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[1] Material presented at March 23, 1977, symposium, Infant Nutrition: A Foundation for Lasting Health?



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Hepatic dysfunction with or without jaundice has occurred, chiefly in adults, in association with erythromycin estolate administration.

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WARNING

Hepatic dysfunction with or without jaundice has occurred, chiefly in adults, in association with erythromycin estolate administration. It may be accompanied by malaise, nausea, vomiting, abdominal colic, and fever. In some instances, severe abdominal pain may simulate an abdominal surgical emergency.

If the above findings occur, discontinue Ilosone promptly.

Ilosone is contraindicated for patients with a known history of sensitivity to this drug and for those with preexisting liver disease.

Indications: Included among the indications for this drug is *Streptococcus pyogenes* (Group A Beta-Hemolytic)—Upper and lower respiratory tract, skin, and soft-tissue infections of mild to moderate severity.

Injectable penicillin G benzathine is considered by the American Heart Association to be the drug of choice in the treatment and prevention of streptococcal pharyngitis and in long-term prophylaxis of rheumatic fever.

When oral medication is preferred for treating the above-mentioned conditions, penicillin G or V or erythromycin is the alternate drug of choice.

The importance of the patient's strict adherence to the prescribed dosage regimen must be stressed when oral medication is given. A therapeutic dose should be administered for at least ten days.

Consult the package literature for other indications.

Contraindication: Known hypersensitivity to this antibiotic.

Warnings: (*See* Warning box above.) The administration of erythromycin estolate has been associated with the infrequent occurrence of cholestatic hepatitis. Laboratory findings have been characterized by abnormal hepatic function test values, peripheral eosinophilia, and leukocytosis. Symptoms may include malaise, nausea, vomiting, abdominal cramps, and fever. Jaundice may or may not be present. In some instances, severe abdominal pain may simulate the pain of biliary colic, pancreatitis, perforated ulcer, or an acute abdominal surgical problem. In other instances, clinical symptoms and results of liver function tests have resembled findings in extrahepatic obstructive jaundice.

Initial symptoms have developed in some cases after a few days of treatment but generally have followed one or two weeks of continuous therapy. Symptoms reappear promptly, usually within 48 hours after the drug is readministered to sensitive patients. The syndrome seems to result from a form of sensitization, occurs chiefly in adults, and has been reversible when medication is discontinued.

Usage in Pregnancy—Safety of this drug for use during pregnancy has not been established.

Precautions: Caution should be exercised in administering the antibiotic to patients with impaired hepatic function.

Surgical procedures should be performed when indicated.

Adverse Reactions: The most frequent side effects are gastrointestinal (e.g., abdominal cramping and discomfort) and are dose related. Nausea, vomiting, and diarrhea occur infrequently with usual oral doses.

During prolonged or repeated therapy, there is a possibility of overgrowth of nonsusceptible bacteria or fungi. If such infections arise, the drug should be discontinued and appropriate therapy instituted.

Mild allergic reactions, such as urticaria and other skin rashes, have occurred. Serious allergic reactions, including anaphylaxis, have been reported.

Administration and Dosage: *Adults*—The usual dosage is 250 mg every six hours. This may be increased up to 4 gm or more per day according to the severity of the infection.

Children—Age, weight, and severity of the infection are important factors in determining the proper dosage. The usual regimen is 30 to 50 mg per kg per day in divided doses. For more severe infections, this dosage may be doubled.

If administration is desired on a twice-a-day schedule in either adults or children, one-half of the total daily dose may be given every 12 hours.

Streptococcal Infections—For the treatment of streptococcal pharyngitis and tonsillitis, the usual dosage range is 20 to 50 mg per kg per day in divided doses.

Body Weight	Total Daily Dose
10 kg or less (less than 25 lb)	250 mg
11-18 kg (25-40 lb)	375 mg
18-25 kg (40-55 lb)	500 mg
25-36 kg (55-80 lb)	750 mg
36 kg or more (more than 80 lb)	1000 mg (adult dose)

In the treatment of group A beta-hemolytic streptococcal infections, a therapeutic dosage of erythromycin should be administered for at least ten days. In continuous prophylaxis of streptococcal infections in persons with a history of rheumatic heart disease, the dosage is 250 mg twice a day.

Consult the package literature for further dosage information.

[060278]

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Letters to the Editor

Adrenal Cortical Carcinoma

Sir.—The observations by Levine (*Am J Dis Child* 132:238-240, 1978) and comments by Miller (*Am J Dis Child* 132:235, 1978) on the curious relationship of adrenal cortical carcinoma in childhood with second primary tumors or dissimilar neoplasms in families emphasizes important considerations for the potential of early detection. Inherent in their concerns were the genetic roots of the patients and families. Environmental influences however, may be virtually impossible to separate from the purely genetic.

The idea that the cancer proneness might be a symbiosis of environment and heredity is not new. This was a consideration when, within six months of diagnosis of adrenal carcinoma in a 7-year-old girl, a medulloblastoma developed in her 4-year-old brother. Despite aggressive surgical and chemotherapeutic treatment, these highly malignant neoplasms resulted in the death of both siblings within a year. The history was unremarkable except that a grandfather and great grandmother had had cancer diagnosed at 65 and 85 years of age, respectively.

It is not apparent from other reports of this curious association of neoplasms whether they more closely coincided in time or with the age of the patients.

Although the genetic apparatus must be at hand, it may well pay off to recognize outside influences capable of triggering such tragic events. We cannot neglect any factors in these peculiar occurrences, since we seem to be at the brink of knowing so much more.

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Differences Between Omphalocele and Gastroschisis

Sir.—Colombani and Cunningham's[1] well-documented series of abdominal wall defects offers some interesting new information about the maternal and perinatal differences between omphalocele and gastroschisis. The pathological findings in their patient group are consistent with numerous other reports in the literature. In their criticism of my article,[2] however, they miss its major point. I do not consider omphalocele and gastroschisis to be the same clinical entity. Indeed, my article emphasizes the clinical differences first pointed out by Moore.[3] "The myth of gastroschisis," to which I refer, does not deny the reality of gastroschisis, but simply seeks to substitute a more rational theory of embryogenesis for those currently in the literature. My point is that although there are clinical differences between gastroschisis and omphalocele and although the factors causing them undoubtedly differ, the clinical evidence suggests that gastroschisis is, like omphalocele and hernia of the umbilical cord (or small omphalocele), an anomaly of the umbilical ring and its coverings. It is not an independent malformation of the lateral abdominal wall.

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1. Colombani PM, Cunningham MD: Perinatal aspects of omphalocele and gastroschisis. *Am J Dis Child* 131:1386-1388, 1977.
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In Reply.—Dr Shaw previously placed a strong argument in the literature for the common origin of omphalocele and gastroschisis. We would have more correctly represented his views if we had quoted him as saying that gastroschisis and omphalocele are the result of failed closure of the umbilical ring, rather than the stated "failed lateral splanchnic fold migration."

The striking clinical differences outlined in our article suggest differing causes (as allowed by Dr Shaw in his letter). If differing etiologies in either an omphalocele or gastroschisis are accepted, why not separate the resulting embryological events? In the absence of an appropriate animal model, the question remains one of failure of closure of the umbilical ring vs a separate and unique failure of migration of the lateral splanchnic fold (usually on the right side), thus resulting in gastroschisis.

Moore[1] has recently reexamined gastroschisis and omphalocele. He does not attempt a unifying theory of dysmorphogenesis. Instead, he also emphasizes the clinical differences of these two entities and sets forth an extensive anatomical classification for each, with six subclassifications.

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1. Moore TC: Gastroschisis and omphalocele: Clinical differences. *Surgery* 82:561-568, 1977.

Adolescent Pregnancy—A National Priority

Sir.—Today, sexual activity has become a prime means of testing one's identity in contemporary adolescents. The significance of this arises from an earlier maturity in which secondary sex characteristics are forceful instigators in achieving one's potential. "Potential" is possibly a better descriptor than "adulthood," for the latter is clouded with contextual differences depending on whether a sociocultural, biophysiological, or psychological index is applied.

It is quite likely that the greatest problem attached to early coitus is not in the act itself but in the dichotomy of values that tend to sway the issue in a right-wrong sense. While it may well be necessary to second-guess the motivation to have sex, ie, requesting permission to be told "no," the problem of adolescent coitus and out-of-wedlock pregnancies are best approached on a continuum of human experience of not necessarily *what* (the act), but *with whom* (the person). At this point, a greater personal attachment in a true human sense can occur, with less interest toward pathological acting-out behavior. In this human context, in which caring for the other receives a prime concern, there is little room for prohibitive Judaeo-Christian "thou shall nots." Also, the emphasis toward prevention—contraception—can be better accepted as a normal and desired means of growth in this area.

The efficacy of the foregoing methodology may not be that great during initiation, which mostly occurs out of curiosity. Nonetheless, it is an appropriate step in the right direction—facing reality and elevating the quality of humanness through respect and concern for the other. Obviously, in those instances in which pregnancy is desired at a young age, the peculiarities of the culture are such as to render counseling useful and pregnancy termination necessary in the interest of the adolescent. Silence as an assumption must yield toward preventive medicine. Conversely, the vociferation of those personifying biomass must be accorded the due respect of their ignorance.

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Pulmonary Perfusion Imaging in Congenital Lobar Emphysema

Sir.— The RADIOLOGICAL CASE OF THE MONTH in a recent issue of the JOURNAL (132:311-312, 1978) is an excellent example of the use of pulmonary perfusion imaging in congenital lobar emphysema. The legend for Fig 2, however, states that the authors are uncertain as to the reason for the activity that was noted within both kidneys. I suggest the following explanation.

Most radiopharmaceuticals enter the systemic circulation after intravenous injection, with subsequent localization within a specific organ in concentrations greater than that of adjacent organs. Lung scanning is unique, however, in that it utilizes particles in the size range of 10 to 20 μ that "embolize" the pulmonary precapillary arterioles. Thus, for particles to be seen in the arterial circulation, there must be a right-to-left cardiac shunt or deficiencies in the preparation of the lung imaging agent.

When smaller particles are present in lung imaging preparation, they traverse the pulmonary vascular bed and hepatic uptake is identified; such uptake is notably absent in Fig 2. Hepatic uptake would not be expected with particles that lodge in the first capillary bed they enter since hepatic perfusion is primarily venous and thus particles become lodged within the splanchnic circulation. Also of note is the fact that the spleen is not seen in Fig 2. This may reflect differences in perfusion to the kidneys and spleen, but raises the possibility of an associated hyposplenism or asplenia in this patient, who very likely has a right-to-left cardiac shunt.

J. C. Leonard, MD
Nuclear Med Service
Oklahoma City, Okla

In Reply.—We share Dr Leonard's opinion that the activity seen within both kidneys (Fig 2) could suggest either a right-to-left cardiac shunt or deficiencies in the preparation of the lung-imaging agent.

Before submitting the manuscript, we carefully examined the patient for possible congenital heart disease, that condition having been reported to be associated with congenital lobar emphysema.[1] We found no clinical evidence of heart involvement; however, definitive heart studies were not done in this patient. We also did not find substantiating evidence for an associated hyposplenism or asplenia. The patient's RBC morphology was normal; findings on sickle cell preparation were negative and no Howell-Jolly bodies were seen in the peripheral blood smear.

One additional point might be made concerning abdominal organ visualization. Take-up of radioactive material in abdominal organs can be explained on the basis of breakage of the bondage of the radioactive compound, with subsequent transmission through the pulmonary-vascular bed. The apparent disparity between the observed activity in the kidney and the expected activity in the liver and spleen may also have resulted from instrument cut-off setting, whereby the higher concentration of deteriorated radioactive material in the kidney (with its greater vascular supply), would be demonstrated, but the lower concentration in the liver and spleen would not be.

We again emphasize the original reason for presenting this case which was to point out the value of perfusion lung scanning in the noninvasive assessment of regional involvement in pulmonary parenchymal disease.[2]

Kwang Sik Kim, MD
E. Thomas Sproles III, MD
New Orleans

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ACTIONS: Theophylline, 1,3-dimethylxanthine, is a bronchodilator. It is rapidly absorbed when given as an elixir. It acts by inhibiting the enzyme phosphodiesterase which degrades cyclic AMP. Its plasma half-life (T½) varies widely because of differences in the rate of metabolism.

Theophylline relaxes the smooth muscle of the respiratory tract and relieves bronchospasm. Its bronchodilator effect is minimal in the absence of bronchospasm.

INDICATIONS: For the relief of bronchial asthma (acute or chronic) and reversible bronchospasm associated with obstructive pulmonary diseases such as chronic bronchitis and emphysema.

Corticosteroids may be given in conjunction with theophylline, if needed.

CONTRAINDICATIONS: Patients with peptic ulcers, active gastritis, and hypersensitivity or idiosyncrasy to theophylline and other methyl xanthines.

WARNINGS: Should not be given concomitantly with other xanthine-containing drugs or liquids (tea, coffee, etc.) because of the potential for serious toxicity from elevated xanthine serum levels.

Use in Pregnancy: Safety has not been established. Theophylline is excreted in the milk.

PRECAUTIONS: Use with caution in patients with cardiovascular disease, in young children and the elderly, and in patients with liver, kidney and heart disease.

ADVERSE REACTIONS: **Gastrointestinal:** loss of appetite, nausea, vomiting, gastric irritation. CNS: irritability, especially in children, insomnia, headache, dizziness, convulsions. These side effects are usually associated with high theophylline serum levels (exceeding 20 μg/ml.) **Cardiovascular:** palpitations, sinus tachycardia and increased pulse rate, usually mild and transient.

Other side effects may include increased irritation with dehydration, muscle twitching and increased SGOT levels.

DRUG INTERACTIONS: Theophylline increases the excretion of lithium carbonate and may enhance the sensitivity and toxicity of digitalis derivatives and sympathomimetic amines. Doses higher than usual may increase the effect of oral anticoagulants. Concomitant use with erythromycin, clindamycin, lincomycin and troleandomycin may increase theophylline serum levels. Colorimetric methods for serum uric acid are affected by theophylline. Spectrophotometric methods for theophylline in serum are affected by furosemide, sulfathiazole, phenylbutazone, probenecid and theobromine.

DOSAGE AND ADMINISTRATION: Dosage must be individualized. Accepted therapeutic serum levels of theophylline are 10-20 μg/ml. Its metabolism may vary greatly with age, among individuals and in patients with liver, kidney and heart disease. Metabolism may be stable with the same individual. However, careful monitoring for manifestations of toxicity and periodic determinations of theophylline serum levels are necessary, especially for prolonged therapy and when using doses higher than 4 mg/kg/6 hours.

Children: The usual starting dose is 4 mg/kg body weight every 6 hours.

The following table may be used with the Dow graduated measuring spoon:

Body Weight		Dose/6 hours		
lbs.	Kgs.	3 mg/kg	4 mg/kg	5 mg/kg
20	9.0	3 ml	4 ml	5 ml
30	14.0	4 ml	6 ml	7 ml
40	18.0	5 ml	7 ml	9 ml
50	23.0	7 ml	9 ml	12 ml
60	27.0	8 ml	11 ml	14 ml
70	32.0	10 ml	13 ml	16 ml
80	36.0	11 ml	14 ml	18 ml
90	41.0	12 ml	16 ml	20 ml
100	45.0	14 ml	18 ml	20 ml

Monitoring of side effects and serum levels is necessary because of the wide variations of theophylline metabolism in children.

Adults: Recommended starting dose is 100 to 200 mg (2 to 4 teaspoonfuls or 10 to 20 ml) every 6 hours. The adequacy of the dose should be determined by clinical response of periodic monitoring of theophylline serum levels.

May be given after meals with water to minimize possible G.I. irritation.

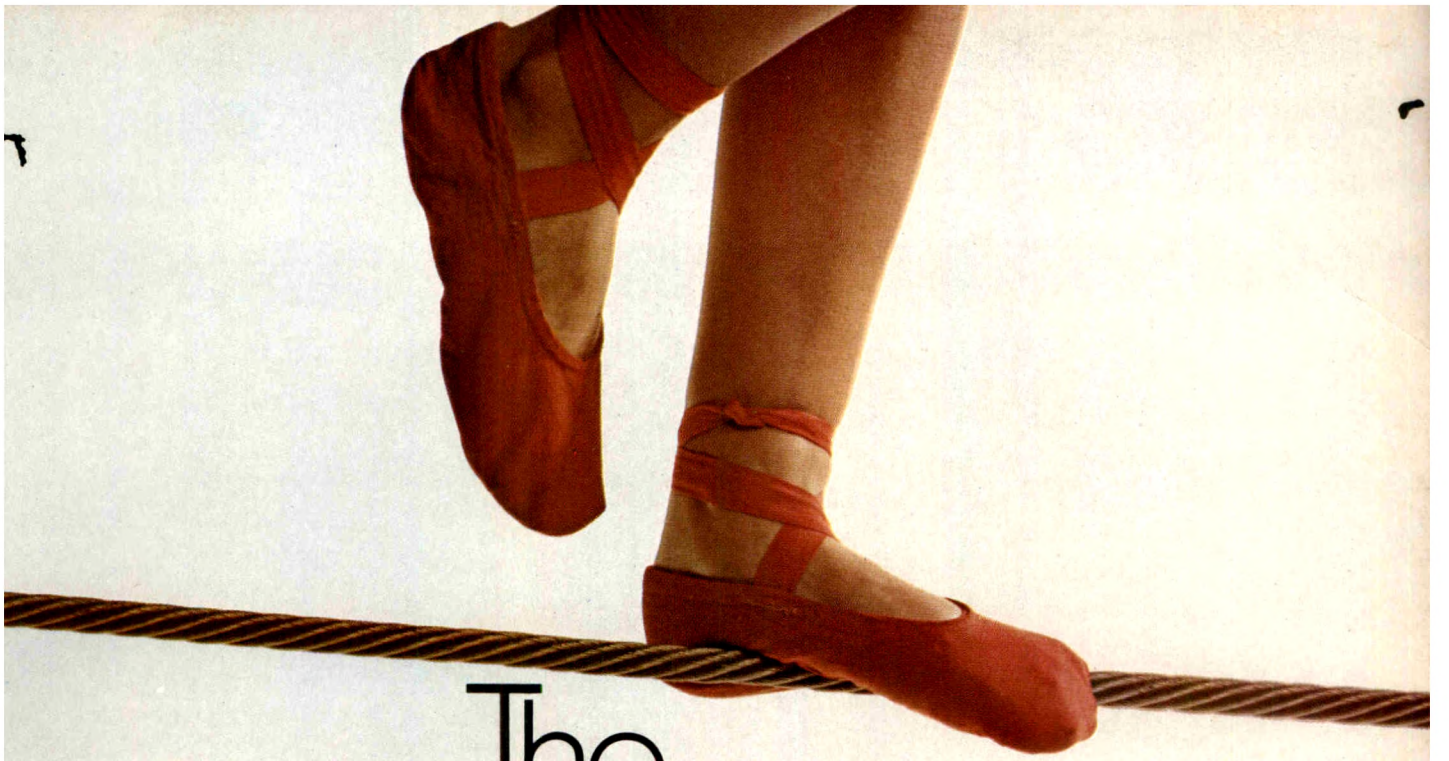
OVERDOSAGE: Theophylline has a narrow therapeutic index and toxicity is likely to occur when serum levels exceed 20 μg/ml. Usual signs of overdosage are anorexia, nausea, vomiting, irritability, headache. Gross overdosage, especially in children, may lead to seizures and death without preceding symptoms of toxicity. Treatment is symptomatic (prompt induction of emesis and gastric lavage, supportive therapy, hemodialysis, etc.).

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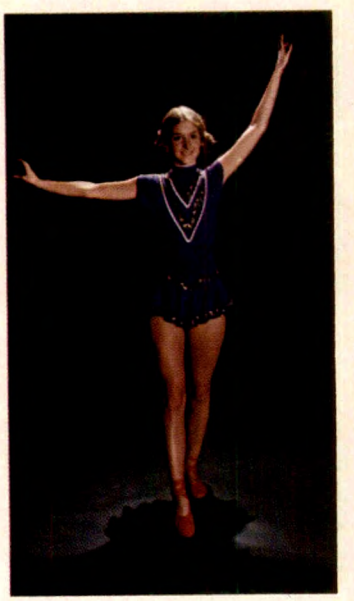
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Adverse Reactions: Occasional drowsiness, blurred vision, cardiac palpitations, flushing, dizziness, nervousness or gastrointestinal upsets.

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American Journal of Diseases of Children

Established 1911

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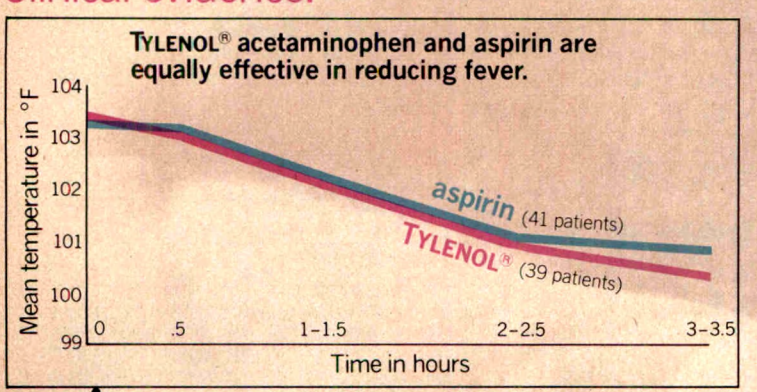
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Warning: Use in Pregnancy: Experience with this drug in pregnant women is inadequate to determine whether there exists a potential for harm to the developing fetus.

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Hepatic dysfunction with or without jaundice has occurred, chiefly in adults, in association with erythromycin estolate administration.

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Brief Summary.
Consult the package literature for prescribing information.

WARNING

Hepatic dysfunction with or without jaundice has occurred, chiefly in adults, in association with erythromycin estolate administration. It may be accompanied by malaise, nausea, vomiting, abdominal colic, and fever. In some instances, severe abdominal pain may simulate an abdominal surgical emergency.

If the above findings occur, discontinue Ilosone promptly.

Ilosone is contraindicated for patients with a known history of sensitivity to this drug and for those with preexisting liver disease.

Indications: Included among the indications for this drug is *Streptococcus pyogenes* (Group A Beta-Hemolytic)—Upper and lower respiratory tract, skin, and soft-tissue infections of mild to moderate severity.

Injectable penicillin G benzathine is considered by the American Heart Association to be the drug of choice in the treatment and prevention of streptococcal pharyngitis and in long-term prophylaxis of rheumatic fever.

When oral medication is preferred for treating the above-mentioned conditions, penicillin G or V or erythromycin is the alternate drug of choice.

The importance of the patient's strict adherence to the prescribed dosage regimen must be stressed when oral medication is given. A therapeutic dose should be administered for at least ten days.

Consult the package literature for other indications.

Contraindication: Known hypersensitivity to this antibiotic.

Warnings: (*See* Warning box above.) The administration of erythromycin estolate has been associated with the infrequent occurrence of cholestatic hepatitis. Laboratory findings have been characterized by abnormal hepatic function test values, peripheral eosinophilia, and leukocytosis. Symptoms may include malaise, nausea, vomiting, abdominal cramps, and fever. Jaundice may or may not be present. In some instances, severe abdominal pain may simulate the pain of biliary colic, pancreatitis, perforated ulcer, or an acute abdominal surgical problem. In other instances, clinical symptoms and results of liver function tests have resembled findings in extrahepatic obstructive jaundice.

Initial symptoms have developed in some cases after a few days of treatment but generally have followed one or two weeks of continuous therapy. Symptoms reappear promptly, usually within 48 hours after the drug is readministered to sensitive patients. The syndrome seems to result from a form of sensitization, occurs chiefly in adults, and has been reversible when medication is discontinued.

Usage in Pregnancy—Safety of this drug for use during pregnancy has not been established.

Precautions: Caution should be exercised in administering the antibiotic to patients with impaired hepatic function.

Surgical procedures should be performed when indicated.

Adverse Reactions: The most frequent side effects are gastrointestinal (e.g., abdominal cramping and discomfort) and are dose related. Nausea, vomiting, and diarrhea occur infrequently with usual oral doses.

During prolonged or repeated therapy, there is a possibility of overgrowth of nonsusceptible bacteria or fungi. If such infections arise, the drug should be discontinued and appropriate therapy instituted.

Mild allergic reactions, such as urticaria and other skin rashes, have occurred. Serious allergic reactions, including anaphylaxis, have been reported.

Administration and Dosage: *Adults*—The usual dosage is 250 mg every six hours. This may be increased up to 4 gm or more per day according to the severity of the infection.

Children—Age, weight, and severity of the infection are important factors in determining the proper dosage. The usual regimen is 30 to 50 mg per kg per day in divided doses. For more severe infections, this dosage may be doubled.

If administration is desired on a twice-a-day schedule in either adults or children, one-half of the total daily dose may be given every 12 hours.

Streptococcal Infections—For the treatment of streptococcal pharyngitis and tonsillitis, the usual dosage range is 20 to 50 mg per kg per day in divided doses.

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25-36 kg (55-80 lb)	750 mg
36 kg or more (more than 80 lb)	1000 mg (adult dose)

In the treatment of group A beta-hemolytic streptococcal infections, a therapeutic dosage of erythromycin should be administered for at least ten days. In continuous prophylaxis of streptococcal infections in persons with a history of rheumatic heart disease, the dosage is 250 mg twice a day.

Consult the package literature for further dosage information.

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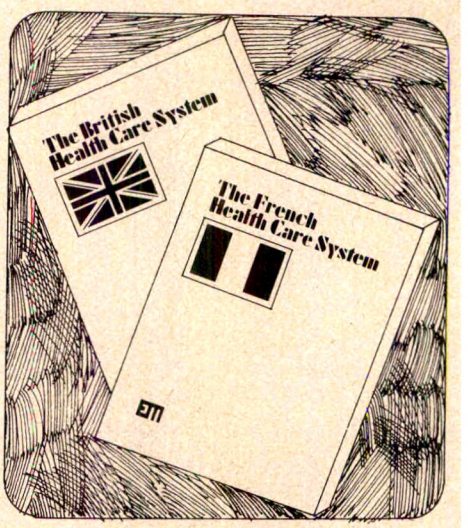
will stop uncomplicated nausea and vomiting

William H. Rorer, Inc., Fort Washington, Pa. 19034

ROER

in depth studies of the health care systems of Britain and France...

how they operate
and what they mean
to users and to people
who work in them.



These highly readable, comprehensive studies, prepared by a London research firm and published by the American Medical Association, offer an opportunity to examine other system's organization, problems, and achievements.

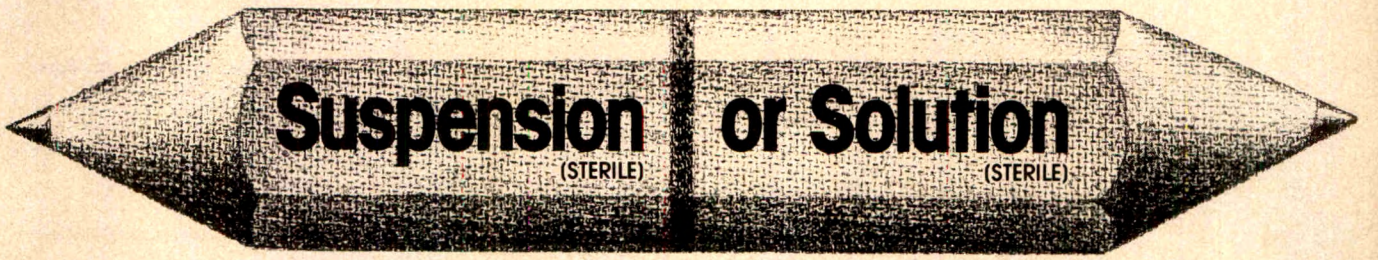
You'll learn how and why the present systems evolved...how they are financed...the range and quality of services available...the training and distribution of medical personnel ...and what effects each system has had upon the health of the general population.

Everyone in the medical profession should read both of these fascinating studies on how other nations have organized the delivery of health care.

Both books will be available Fall of 1976. To order your copies, write ORDER DEPT., AMA, 535 N. DEARBORN ST., CHICAGO, ILL. 60610. **The French Health Care System** (OP-460) costs $3.50; the **British Health Care System** (OP-461), $7.50. The set is $10. Remittance must accompany order.

Please don't just Rx "Cortisporin® Otic"...Specify:

(polymyxin B-neomycin-hydrocortisone)



INDICATIONS:
For the treatment of superficial bacterial infections of the external auditory canal caused by organisms susceptible to the action of the antibiotics, and for the treatment of infections of mastoidectomy and fenestration cavities caused by organisms susceptible to the antibiotics.

DESCRIPTION:
Each cc contains: Aerosporin® brand
Polymyxin B Sulfate ..... 10,000 units
Neomycin Sulfate ..... 5 mg
(equivalent to 3.5 mg neomycin base)
Hydrocortisone ..... 10 mg (1%)
The vehicle contains the inactive ingredients cetyl alcohol, propylene glycol, polysorbate 80, purified water and thimerosal (preservative) 0.01%.

PRECAUTIONS:
This drug should be used with care in cases of perforated eardrum and in long-standing cases of chronic otitis media because of the possibility of ototoxicity caused by neomycin.

ADVERSE REACTIONS:
Neomycin is a not uncommon cutaneous sensitizer. There are articles in the current literature that indicate an increase in the prevalence of persons sensitive to neomycin.

BENEFITS:
Indications include infections of mastoidectomy and fenestration cavities caused by organisms susceptible to the antibiotics.

INDICATIONS:
For the treatment of superficial bacterial infections of the external auditory canal caused by organisms susceptible to the action of the antibiotics.

DESCRIPTION:
Each cc contains: Aerosporin® brand
Polymyxin B Sulfate ..... 10,000 units
Neomycin Sulfate ..... 5 mg
(equivalent to 3.5 mg neomycin base)
Hydrocortisone ..... 10 mg (1%)
The vehicle contains the inactive ingredients glycerin, hydrochloric acid, propylene glycol, purified water and potassium metabisulfite (preservative) 0.1%.

PRECAUTIONS:
This drug should be used with care when the integrity of the tympanic membrane is in question because of the possibility of ototoxicity caused by neomycin.

ADVERSE REACTIONS:
Neomycin is a not uncommon cutaneous sensitizer. There are articles in the current literature that indicate an increase in the prevalence of persons sensitive to neomycin. Stinging and burning have been reported when this drug has gained access to the middle ear.

BENEFITS:
Clear visualization of field. Does not have to be shaken.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS COMMON TO BOTH PRODUCTS:

CONTRAINDICATIONS:
In individuals who have shown hypersensitivity to any of the components, and in herpes simplex, vaccinia, and varicella.

WARNINGS:
Prolonged treatment may result in overgrowth of non-susceptible organisms and fungi. If the infection is not improved after one week, cultures and susceptibility tests should be repeated to verify the identity of the organism, and to determine whether therapy should be changed.

When using neomycin-containing products to control secondary infection in the chronic dermatoses, such as otitis externa, it should be borne in mind that the skin in these conditions is more liable than is normal skin to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling, and itching; it may be manifest simply as a failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

PRECAUTIONS:
If sensitization or irritation occurs, medication should be discontinued promptly. Patients who prefer to warm the medication before using should be cautioned against heating the solution above body temperature, in order to avoid loss of potency.

Treatment should not be continued for longer than ten days. Allergic cross-reactions may occur which could prevent the use of any or all of the following antibiotics for the treatment of future infections: kanamycin, paromomycin, streptomycin, and possibly gentamicin.

HOW SUPPLIED:
Both products available in 10 cc bottles with sterile droppers.

Both products offer you:

- Wide range of antibacterial activity, including action against many strains of *Pseudomonas aeruginosa* and *Proteus*.
- Direct anti-inflammatory action, relieving associated itching, swelling and pain.
- Economy for your patients.

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Name_____

Address_____

City/State/Zip_____

ACCURBRON™
theophylline

DESCRIPTION: Each ml contains anhydrous theophylline 10 mg (50 mg per 5 ml teaspoonful) and alcohol 7.5% in a pleasant tasting vehicle.

ACTIONS: Theophylline, 1, 3-dimethylxanthine, is a bronchodilator. It is rapidly absorbed when given as an elixir. It acts by inhibiting the enzyme phosphodiesterase which degrades cyclic AMP. Its plasma half-life (T ½) varies widely because of differences in the rate of metabolism.

Theophylline relaxes the smooth muscle of the respiratory tract and relieves bronchospasm. Its bronchodilator effect is minimal in the absence of bronchospasm.

Other actions of theophylline include dilation of pulmonary, coronary and renal arteries and increased cardiac output, and CNS stimulation. Usual doses increase blood pressure only slightly. Theophylline also has a mild diuretic action.

INDICATIONS: For the relief of bronchial asthma (acute or chronic) and reversible bronchospasm associated with obstructive pulmonary diseases such as chronic bronchitis and emphysema.

Theophylline relieves the shortness of breath, wheezing and dyspnea associated with asthma and improves pulmonary function (increases flow rates and vital capacity). In doses sufficient to produce therapeutic serum concentrations (10-20 μg/ml), theophylline would also prevent the symptoms of chronic asthma and suppress exercise-induced asthma. It is especially useful for long-term treatment of bronchospasm because tolerance to the bronchodilator effect of theophylline rarely occurs.

Corticosteroids may be given in conjunction with theophylline, if needed.

CONTRAINDICATIONS: Patients with peptic ulcers, active gastritis, and hypersensitivity or idiosyncrasy to theophylline and other methylxanthines.

WARNINGS: Should not be given concomitantly with other xanthine-containing drugs because of the potential for serious toxicity from elevated xanthine serum levels. Also, liquids containing xanthines (tea, coffee, etc.) should be avoided.

Use in Pregnancy: Safety for use during pregnancy has not been established. Theophylline is excreted in the milk. Use during lactation and in women of childbearing potential requires that benefits be weighed against possible hazards to fetus or child.

PRECAUTIONS: As with all theophylline-containing products, use with caution in patients with cardiovascular disease, in infants and the elderly, and in patients with liver, kidney and heart disease.

ADVERSE REACTIONS: **Gastrointestinal:** loss of appetite, nausea, vomiting, gastric irritation. **CNS:** irritability, especially in children, insomnia, headache, dizziness, convulsions. These side-effects are usually associated with high theophylline serum levels (exceeding 20 μg/ml). **Cardiovascular:** palpitations, sinus tachycardia and increased pulse rate, usually mild and transient.

Other side-effects may include increased irritation with dehydration, muscle twitching and increased SGOT levels.

DRUG INTERACTIONS: Theophylline increases the excretion of lithium carbonate and may enhance the sensitivity and toxicity of digitalis derivatives and sympathomimetic amines. Doses higher than usual may increase the effect of oral anticoagulants. Concomitant use with erythromycin, clindamycin, lincomycin and troleandomycin may increase theophylline serum levels.

Colorimetric methods for serum uric acid are affected by theophylline. Spectrophotometric methods of theophylline in serum are affected by furosemide, sulfathiazole, phenylbutazone, probenecid and theobromine.

DOSAGE AND ADMINISTRATION: Dosage must be individualized. Accepted therapeutic serum levels for theophylline are 10-20 μg/ml. Its metabolism may vary greatly with age, among individuals and in patients with liver, kidney and heart disease. Metabolism may be stable within the same individual. However, careful monitoring for manifestations of toxicity and periodic determinations of theophylline serum levels are necessary, especially for prolonged therapy and with high doses.

Children: The following table may be used with the graduated measuring spoon for Accurbron:

ACCURBRON™ (theophylline) — PEDIATRIC DOSAGE CALCULATION TABLE

Starting dosage[1]: (All ages for first 3 days[2]) **4 mg/kg body wt every 6 hours not to exceed 100 mg (10 ml Accurbron)**

Age	Body Weight		Dose/6 hours				
	lbs	kgs	3 mg/kg	4 mg/kg	5 mg/kg	6 mg/kg	7 mg/kg
Under 9 years*	10	4.5	1 ml	2 ml	2 ml	3 ml	3 ml
average dose	20	9	3 ml	4 ml	5 ml	5 ml	6 ml
4-6 mg/kg/6 hrs.[1]	30	14	4 ml	6 ml	7 ml	8 ml	10 ml
	40	18	5 ml	7 ml	9 ml	11 ml	13 ml
	50	23	7 ml	9 ml	12 ml	14 ml	16 ml
	60	27	8 ml	11 ml	14 ml	16 ml	19 ml
	70	32	10 ml	13 ml	16 ml	19 ml	22 ml
9-12 years*	80	36	11 ml	14 ml	18 ml	22 ml	25 ml
average dose	90	41	12 ml	16 ml	20 ml	25 ml	29 ml
4-5 mg/kg/6 hrs.[1]	100	45	14 ml	18 ml	22 ml	27 ml	32 ml

ACCURBRON contains 10 mg theophylline (anhydrous) per ml.

1. Average dosage from: Wyatt R, Weinberger M, Hendeles L: Oral theophylline dosage for the management of chronic asthma. **J Ped 92:** 125-130,1978.
2. Mitenko PA, Ogilvie RI: Rapidly achieved plasma concentration plateaus, with observations on theophylline kinetics. **Clin Pharmacol Therap 13:** 329-335, 1972.

*Do not exceed this dosage without careful clinical monitoring or checking theophylline serum level because of the increased risk of side effects when serum levels exceed 20 μg/ml.

Adults: Recommended starting dose is 100 to 200 mg (10 to 20 ml) every 6 hours. The adequacy of the dose should be determined by clinical response and periodic monitoring of theophylline serum levels.

May be given after meals with water to minimize possible G.I. irritation.

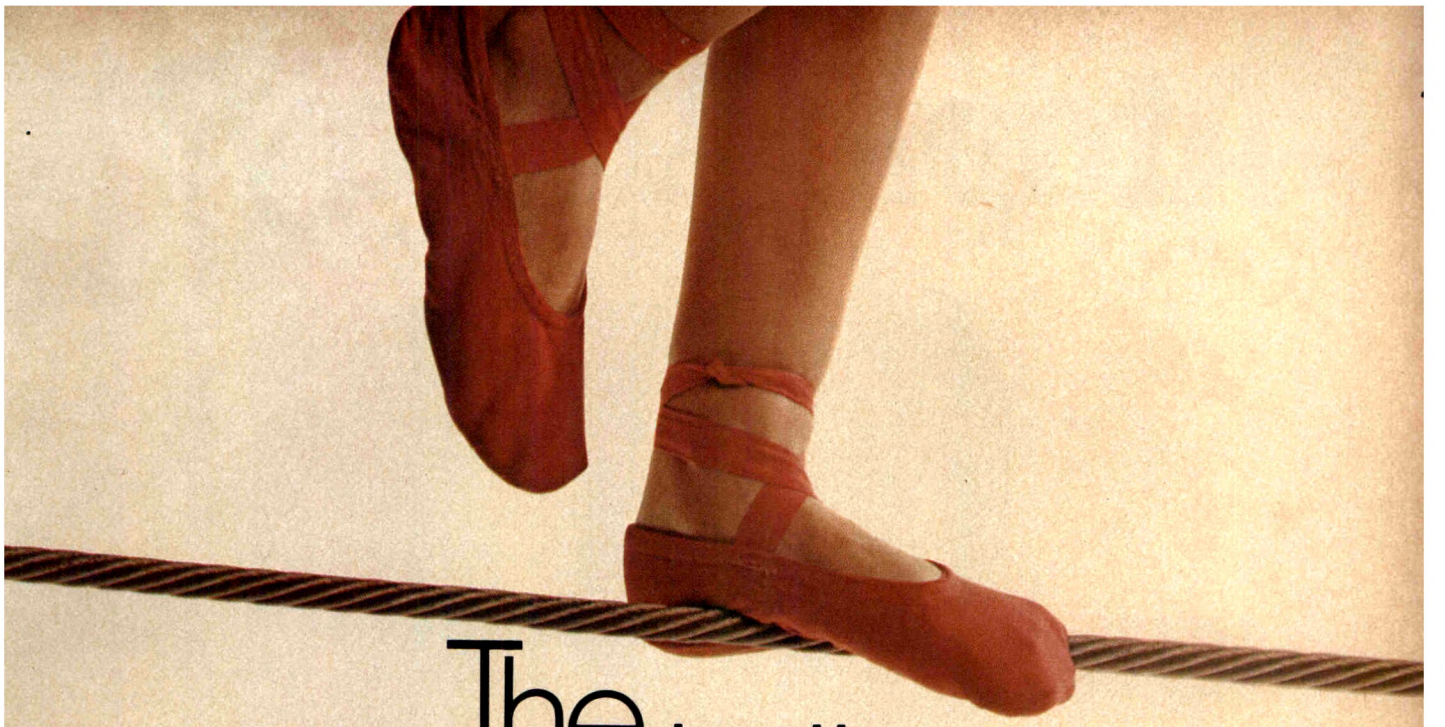
OVERDOSAGE: Theophylline has a narrow therapeutic index and toxicity is likely to occur when serum levels exceed 20 μg/ml. Usual signs of overdosage are anorexia, nausea, vomiting, irritability, headache. Gross overdosage, especially in children, may lead to seizures and death without preceding symptoms of toxicity. Treatment is symptomatic (prompt induction of emesis and gastric lavage, supportive therapy, hemodialysis, etc.).

CAUTION: Federal law prohibits dispensing without prescription.

HOW SUPPLIED: As a dye-free liquid in pint bottles (NDC 0183-5002-05) withthe graduated measuring spoon for Accurbron.

DOW

Dow Pharmaceuticals
The Dow Chemical Company
Indianapolis, Indiana 46268



The Theophylline tightrope.

Maintain the balance with Accurbron.

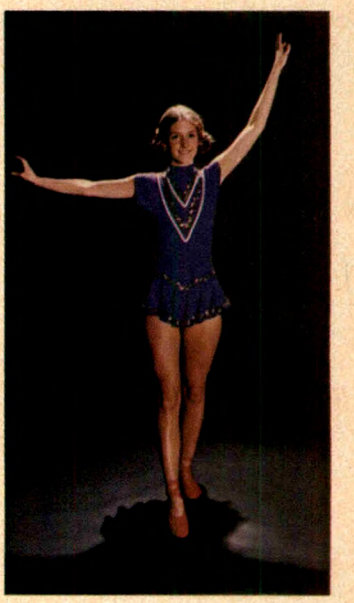
In theophylline therapy, the therapeutic range is narrow. Serum levels in the 10 mcg/ml to 20 mcg/ml range are necessary for optimum effect with minimal side effects. Accurbron offers an effective bronchodilator for the symptomatic relief of bronchial asthma with simplified delivery system for more accurate dosage.

For easy dosage calculation, each milliliter of Accurbron contains 10 mg. anhydrous theophylline. Then, for precise measurement, a special combination spoon and vial is calibrated to deliver the measured dose of Accurbron.*

And, with the acceptable, neutral flavor of Accurbron flavor fatigue is less likely to occur.



*A combination spoon and vial, graduated in milliliters to assure more accurate dosage, is packed with each pint bottle of Accurbron.



ACCURBRON™
theophylline

Each ml. contains anhydrous theophylline 10 mg. and alcohol 7.5%

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Dow Pharmaceuticals
The Dow Chemical Company
Indianapolis, Indiana 46268

See opposite page for prescribing information

Atopic Allergy?



a hereditary predisposition?

"In children with a double parental history of atopic disease the incidence of such disease was higher than in children with a single such heredity in whom, however, the incidence was higher than in children without any parental history of atopic disease."

When history and examination are equivocal the use of IgE as a parameter for atopic allergy either for diagnostic or predictive purposes should be decisive.

Kjellman, N-I Max: Immunoglobulin E and Atopic Allergy in Children. Linköping University Medical Dissertations 36, 1976.

Phadebas IgE PRIST®

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The test to predict atopic allergies in children.

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New space-saving packaging
Easy to store in refrigerator.



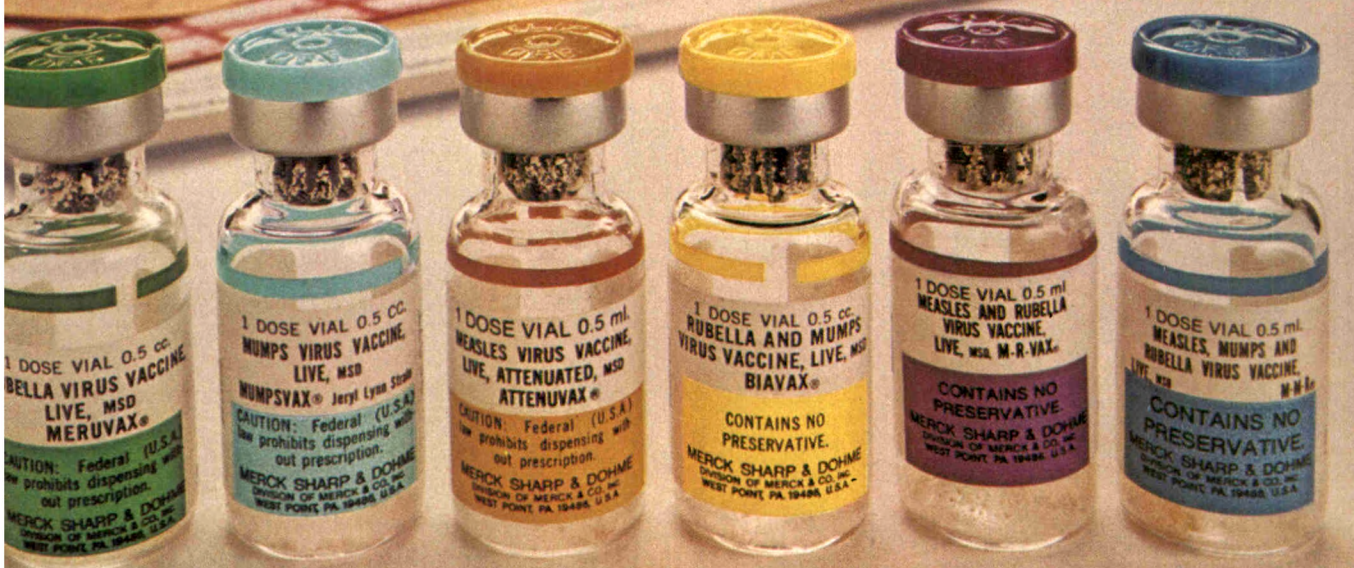
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Provides parents with a record at a glance of vaccines given to date.



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For instant identification.



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(Rubella and Mumps Virus Vaccine, Live|MSD)

SINGLE-DOSE VIALS
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SINGLE-DOSE VIALS
M-M-R®
(Measles, Mumps and Rubella Virus Vaccine, Live|MSD)

Backing up our line of pediatric vaccines is an integrated system from Merck Sharp & Dohme

For more details about the MSD vaccine system, please see your MSD Representative.

For a brief summary of prescribing information, please see following page.

MSD
MERCK SHARP & DOHME

pediatric vaccines from Merck Sharp & Dohme

Indications: *ATTENUVAX® (Measles Virus Vaccine, Live, Attenuated, MSD)*—Active immunization against measles (rubeola) in children 15 months of age or older.

BIAVAX® (Rubella and Mumps Virus Vaccine, Live, MSD)—Simultaneous immunization against rubella and mumps in children 15 months of age to puberty. May be given as early as 12 months if that offers greater convenience in scheduling.

MERUVAX® (Rubella Virus Vaccine, Live, MSD)—Immunization against rubella (German measles) in children 15 months of age to puberty. May be given as early as 12 months if that offers greater convenience in scheduling. May be useful for postpubertal males to prevent or control rubella outbreaks in circumscribed population groups. In postpubertal females vaccination must not be undertaken unless the woman is not pregnant, is susceptible to rubella (as shown by Hemagglutination Inhibition test), understands it is imperative not to become pregnant for next three months and will follow a medically acceptable method for pregnancy prevention (also in immediate postpartum period), and is informed of frequent occurrence of self-limited arthralgia and possible arthritis beginning two to four weeks after vaccination.

M·M·R® (Measles, Mumps and Rubella Virus Vaccine, Live, MSD)—Simultaneous immunization against measles, mumps, and rubella in children 15 months of age to puberty.

M·R·VAX® (Measles and Rubella Virus Vaccine, Live, MSD)—Simultaneous immunization against measles (rubeola) and rubella (German measles) in children 15 months of age to puberty.

MUMPSVAX® (Mumps Virus Vaccine, Live, MSD)—Immunization against mumps for children 15 months of age or older and adults. May be given as early as 12 months if that offers greater convenience in scheduling.

Contraindications: Pregnancy or the possibility of pregnancy within three months following vaccination (see special considerations for ATTENUVAX below); hypersensitivity to neomycin; in patients hypersensitive to chicken or chicken eggs or feathers or, for rubella-containing vaccines, duck or duck eggs or feathers, weigh benefits of immunization against potential risks of hypersensitivity reactions; any febrile respiratory illness or other active infection; for measles-containing vaccines, active untreated tuberculosis; therapy with ACTH, corticosteroids (except as replacement therapy, e.g., for Addison's disease), irradiation, alkylating agents, or antimetabolites; blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems; primary immunodeficiency states, including cellular immune deficiencies, hypogammaglobulinemic, and dysgammaglobulinemic states.

ATTENUVAX—PREGNANCY: The effects of ATTENUVAX on fetal development are unknown at this time. Live attenuated measles virus vaccine should not be given to persons known to be pregnant; furthermore, pregnancy should be avoided for three months following vaccination. Reports have indicated that natural measles during pregnancy enhances fetal risk. Increased rates of spontaneous abortion, stillbirth, congenital defects, and prematurity have been observed subsequent to natural measles during pregnancy. There are no adequate studies of the attenuated (vaccine) strain of measles virus in pregnancy. However, it would be prudent to assume that the vaccine strain of virus is also capable of inducing adverse fetal effects for up to three months following vaccination.

Vaccine administration to post-pubertal females entails a potential for inadvertent immunization during pregnancy. Theoretical risks involved should be weighed against the risks that measles poses to the unimmunized adolescent or adult. Advisory committees reviewing this matter have recommended vaccination of post-pubertal females who are presumed to be susceptible to measles and not known to be pregnant. If a measles exposure occurs during pregnancy, one should consider the possibility of providing temporary passive immunity through the administration of immune serum globulin (human).

Precautions: Administer subcutaneously; *do not give intravenously*. Epinephrine should be available for immediate use should an anaphylactoid reaction occur. Should not be given less than one month before or after immunization with other *live* virus vaccines, with the exception of monovalent or trivalent poliovirus vaccine, live, oral, which may be administered simultaneously. Vaccinations should be deferred for at least three months following blood or plasma transfusions or administration of more than 0.02 ml human immune serum globulin per pound of body weight. Rubella vaccine may be given in the immediate postpartum period to those nonimmune women who have received anti-Rh_0 (D) immune globulin (human) without interfering with vaccine effectiveness.

Attenuated measles, mumps, and rubella virus vaccines, live, given separately, may result in a temporary depression of tuberculin skin sensitivity; therefore, if a tuberculin test is to be done, it should be administered before or simultaneously with any of these virus vaccines.

Measles-Containing Vaccines—Due caution should be employed in children with a history of febrile convulsions, cerebral injury, or any other condition in which stress due to fever should be avoided. The physician should be alert to the temperature elevation which may occur 5 to 12 days after vaccination. The occurrence of thrombocytopenia and purpura has been extremely rare.

Rubella-Containing Vaccines—Excretion of live attenuated rubella virus from the throat has occurred in the majority of susceptible individuals administered rubella vaccine. There is no definitive evidence to indicate that such virus is contagious to susceptible persons who are in contact with vaccinated individuals. Consequently, transmission, while accepted as a theoretical possibility, has not been regarded as a significant risk.

Adverse Reactions: To date, clinical evaluation of the combination vaccines has revealed those adverse reactions expected to follow administration of the monovalent vaccines given separately.

Measles-Containing Vaccines—Occasionally, moderate fever (101-102.9 F); less commonly, high fever (above 103 F); rarely, febrile convulsions. Infrequently, rash, usually minimal without generalized distribution. Reactions at injection site. Local reactions characterized by marked swelling, redness, and vesiculation at the injection site of attenuated live measles virus vaccines have occurred in children who received killed measles vaccine previously; the combination vaccines were not given under this condition in clinical trials.

Experience from more than 80 million doses of all live measles vaccines given in the U.S. through 1975 indicates that significant central nervous system reactions such as encephalitis and encephalopathy, occurring within 30 days after vaccination, have been temporally associated with measles vaccine approximately once for every million doses. In no case has it been shown that reactions were actually caused by vaccine. The Center for Disease Control has pointed out that "a certain number of cases of encephalitis may be expected to occur in a large childhood population in a defined period of time even when no vaccines are administered." However, the data suggest the possibility that some of these cases may have been caused by measles vaccines. The risk of such serious neurological disorders following live measles virus vaccine administration remains far less than that for encephalitis and encephalopathy with natural measles (one per thousand reported cases). There have been reports of subacute sclerosing panencephalitis (SSPE) in children who did not have a history of natural measles but did receive measles vaccine. Some of these cases may have resulted from unrecognized measles in the first year of life or possibly from the measles vaccination. Based on estimated nationwide measles vaccine distribution, the association of SSPE cases to measles vaccination is about one case per million vaccine doses distributed, far less than the 5-10 cases of SSPE per million cases of natural measles.

Rubella-Containing Vaccines—Adverse reactions may include fever and rash; mild local reactions such as erythema, induration, tenderness, and regional lymphadenopathy; thrombocytopenia and purpura; allergic reactions such as urticaria; and arthritis, arthralgia, and polyneuritis.

Moderate fever (101-102.9 F) occurs occasionally, and high fever (103 F) occurs less commonly. Rash occurs infrequently and is usually minimal without generalized distribution. Encephalitis and other nervous system reactions have occurred very rarely.

Transient arthritis, arthralgia, and polyneuritis vary in frequency and severity with age and sex, being greatest in adult females and least in prepubertal children. Symptoms relating to joints (pain, swelling, stiffness, etc.) and to peripheral nerves (pain, numbness, tingling, etc.) occurring within approximately two months after vaccination should be considered as possibly vaccine related. These symptoms need not be associated with other features of rubella, such as fever, rash, and lymphadenopathy. In prepubertal children, the symptoms have generally been mild and of no more than three days' duration, with an incidence of less than 1 percent for reactions that would interfere with normal activity or necessitate medical attention. In teen-age girls, the rates of reactions are somewhat higher but probably do not exceed 5 to 10 percent. In women, the rates are greater and may exceed 30 percent; the symptoms in older females tend to be more prominent and of longer duration, rarely persisting for a matter of months, but have not generally interfered with normal activity. There is, at present, no evidence that the joint involvement or neuritis accompanying infection with either natural rubella or the attenuated viruses predisposes to any of the known chronic arthritic or neurologic diseases. Transient arthralgia and arthritis in nonimmune males may occur; however, as in the natural disease, the incidence is expected to be lower than in women.

Mumps-Containing Vaccines—Parotitis. Rarely, purpura and allergic reactions such as urticaria. Very rarely, encephalitis and other nervous system reactions. With the monovalent mumps vaccine, mild fever occurs occasionally, and fever above 103 F is uncommon.

Shipment, Storage, and Reconstitution: During shipment, to insure that there is no loss of potency, the vaccine must be maintained at a temperature of 10 C (50 F) or less. Before reconstitution, store vaccines at 2-8 C (35.6-46.4 F) and *protect from light*. Use only diluent supplied to reconstitute vaccines. If not used immediately, store reconstituted vaccines in a dark place at 2-8 C (35.6-46.4 F), and discard if not used within eight hours.

Color change: The usual color of the vaccine when reconstituted is pinkish to red due to the presence of phenol red, a pH indicator. Some vaccine which has been shipped in dry ice may exhibit a variation in color when reconstituted because carbon dioxide has been absorbed from the dry ice. This vaccine, if crystal clear on reconstitution, is acceptable for use whether it is red, pink, or yellow.

How Supplied: *ATTENUVAX® (Measles Virus Vaccine, Live, Attenuated, MSD)*—Single-dose vials of lyophilized vaccine, containing when reconstituted not less than 1,000 $TCID_{50}$ (tissue culture infectious doses) of measles virus vaccine expressed in terms of the assigned titer of the FDA Reference Measles Virus, and approximately 25 mcg neomycin.

BIAVAX® (Rubella and Mumps Virus Vaccine, Live, MSD)—Single-dose vials of lyophilized vaccine, containing when reconstituted not less than 1,000 $TCID_{50}$ of rubella virus vaccine, live, and 5,000 $TCID_{50}$ of mumps virus vaccine, live, expressed in terms of the assigned titer of the FDA Reference Rubella and Mumps Viruses, and approximately 25 mcg neomycin.

MERUVAX® (Rubella Virus Vaccine, Live, MSD)—Single-dose vials of lyophilized vaccine, containing when reconstituted not less than 1,000 $TCID_{50}$ of rubella virus vaccine expressed in terms of the assigned titer of the FDA Reference Rubella Virus, and approximately 25 mcg neomycin.

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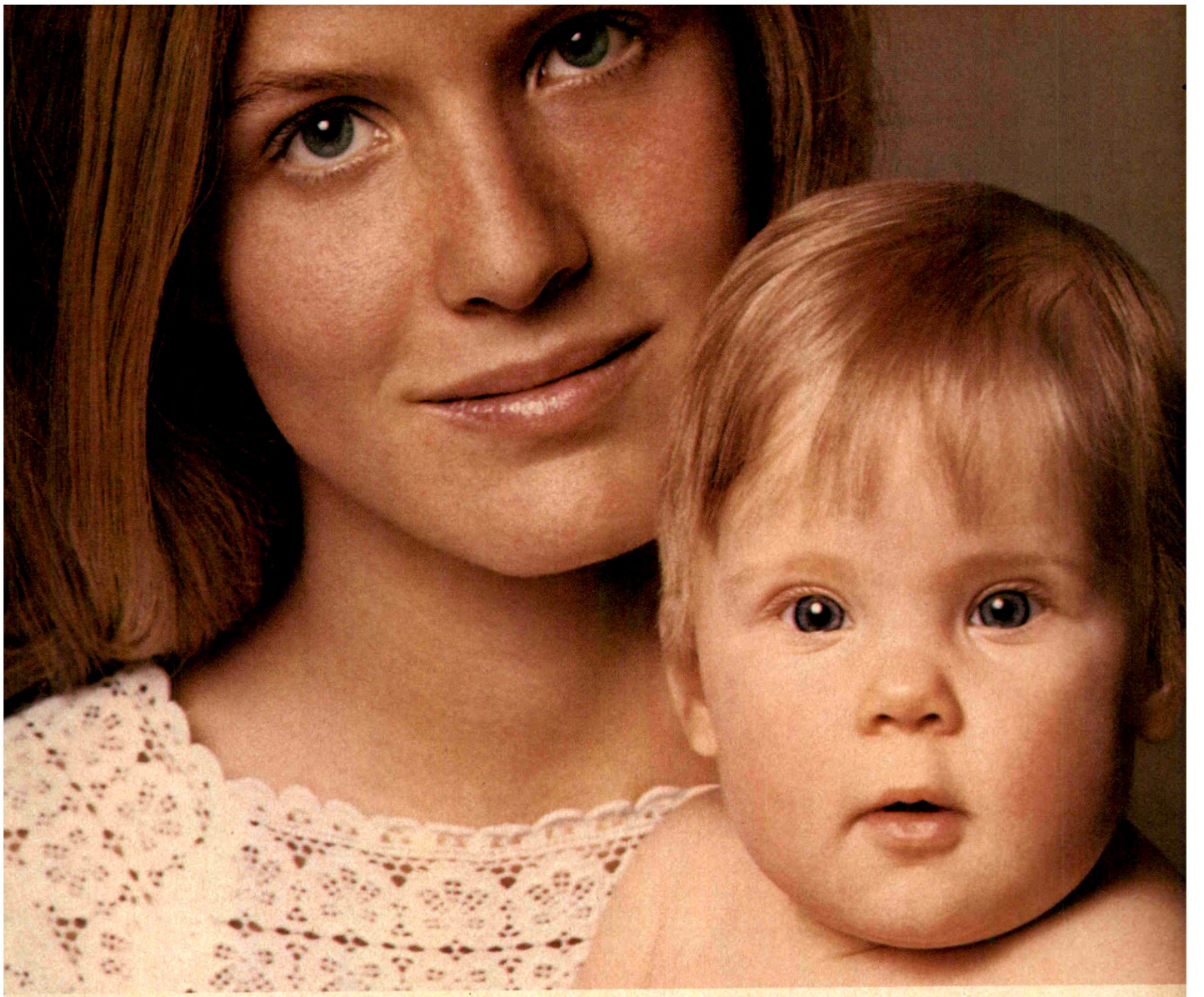
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MUMPSVAX® (Mumps Virus Vaccine, Live, MSD)—Single-dose vials of lyophilized vaccine, containing when reconstituted not less than 5,000 $TCID_{50}$ of mumps virus vaccine expressed in terms of the assigned titer of the FDA Reference Mumps Virus, and approximately 25 mcg neomycin.

Each of these vaccines is supplied as a single-dose vial packed with a disposable syringe containing diluent and fitted with a 25-gauge, 5/8" needle, and as a box of 10 single-dose vials with an accompanying box of 10 diluent-containing disposable syringes with affixed needles.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486. J6VA02R3

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That's why you should specify that new mothers keep their babies on breast milk or infant formula for a full 12 months.

Switching to cow's milk in the first year is not advisable. The high sodium content and the high protein content of cow's milk may increase the risk of dehydration and hypernatremia when diarrhea or other conditions increase the demand for water. Cow's milk feedings may place infants at risk for developing iron deficiency. And cow's milk is a poor source of copper and Vitamin C.[1]

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ENFAMIL infant formula is patterned after breast milk and is a good source of digestible heat-treated protein, polyunsaturated fat, vitamins and minerals.

Recommend ENFAMIL until the end of the first year for infants who aren't breast feeding or who stop breast feeding.



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[1] Material presented at March 23, 1977, symposium, Infant Nutrition: A Foundation for Lasting Health?

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INFANT FORMULA

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When unproductive coughs startle,

HYCOTUSS® Expectorant provides effective antitussive/expectorant action — controls coughing for up to 6 hours and helps liquefy bronchial secretions to aid expectoration.

HYCOTUSS® EXPECTORANT C III

Each teaspoonful (5 ml) contains 5 mg hydrocodone bitartrate (WARNING: May be habit forming), 100 mg guaifenesin and alcohol U.S.P. 10% v/v

Cough relief for children under 12

USUAL DOSAGE: *Children under 2 years* — calculate as hydrocodone, 0.3 mg/kg/24 hours, divided into 4 equal doses. *Children 2 to 12 years* — ½ teaspoonful after meals and at bedtime, not less than 4 hours apart. *Children over 12 and adults* — 1 teaspoonful after meals and at bedtime, not less than 4 hours apart.

Please see brief summary of prescribing information below.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

CONTRAINDICATIONS: HYCOTUSS Expectorant should not be used in patients with hypersensitivity to hydrocodone or guaifenesin.

WARNINGS: HYCOTUSS Expectorant should be prescribed and administered with the same degree of caution appropriate for the use of other oral narcotic-containing medications since it can produce drug dependence and, therefore, has the potential for abuse. Patients should be warned not to drive a car or operate machinery if they become drowsy or show impaired mental and/or physical abilities while taking HYCOTUSS Expectorant. Patients receiving narcotic analgesics, phenothiazines, other tranquilizers, sedative-hypnotics or other central nervous system depressants (including alcohol) concomitantly with HYCOTUSS Expectorant may exhibit an additive central nervous system depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

PRECAUTIONS: Before prescribing medication to suppress or modify cough, it is important to ascertain that the underlying cause of cough is identified, that modification of cough does not increase the risk of clinical or physiologic complications, and that appropriate therapy for the primary disease is provided.

ADVERSE REACTIONS: Adverse reactions, when they occur, include sedation, nausea, vomiting and constipation.

DRUG INTERACTIONS: The central nervous system depressant effects of HYCOTUSS Expectorant may be additive with that of other central nervous system depressants. See WARNINGS.

6072-3

Oral prescription where permitted by State law.

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6070-2BS

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DUPONT



A new indication for Septra

Getting a child with an earache off to sleep is hard enough, without getting her up again. With the q.i.d. and t.i.d. dosages of other antibacterials for acute otitis media, expecting compliance may be expecting a lot. Septra b.i.d. dosage convenience can change all that.

In a study of 94 children with bacterial otitis media confirmed by culture, Septra Suspension produced a success rate of 95.7%.†

Septra Suspension has proved highly effective in acute otitis media caused by the most common middle ear pathogens—*Haemophilus influenzae* and *Streptococcus pneumoniae.*

Though crystalluria has not been a problem with Septra, adequate fluid intake should be maintained and frequent urinalyses with careful microscopic examination performed during therapy. Septra is contraindicated in infants under two months. **Septra should not be used in the treatment of streptococcal pharyngitis.**

†Data on file, Medical Department, Burroughs Wellcome Co.
See last page of this advertisement for prescribing information.



middle-of-the-night" dose
cute otitis media*

Septra®
Suspension

Each teaspoonful (5 ml) contains:
40 mg trimethoprim and 200 mg sulfamethoxazole

b.i.d.

through-the-night efficacy against major middle ear pathogens

*Septra is now indicated for use in acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in the judgment of the physician Septra offers some advantage over the use of other antimicrobial agents. Limited clinical information is presently available on the effectiveness of treatment of otitis media with Septra when the infection is due to *Haemophilus influenzae* resistant to ampicillin. To date, there are limited data on the safety of repeated use of Septra in children under two years of age. Septra is not indicated for prophylactic or prolonged administration in otitis media at any age.



Septra® introduces b.i.d. dosage convenience to the treatment of acute otitis media in children

Septra® Suspension

Each teaspoonful (5 ml) contains:
40 mg trimethoprim and 200 mg sulfamethoxazole

- effective *in vitro* against major middle ear pathogens—*Haemophilus influenzae*, including ampicillin-resistant strains, and *Streptococcus pneumoniae**
- well tolerated by infants and children† (Contraindicated in infants under two months. See brief summary below for possible adverse reactions.)

Septra® Tablets

Each tablet contains:
80 mg trimethoprim and 400 mg sulfamethoxazole

- available in pleasant tasting cherry-flavored suspension or in tablet form for use in older children
- encourages compliance; unlike other antibacterials for otitis media, Septra requires no middle-of-the-night dose

---

Septra® Tablets and Suspension

Indications and Usage:

ACUTE OTITIS MEDIA: **For the treatment of acute otitis media in children due to susceptible strains of** *Haemophilus influenzae* **or** *Streptococcus pneumoniae* **when in the judgment of the physician Septra offers some advantage over the use of other antimicrobial agents. Limited clinical information is presently available on the effectiveness of treatment of otitis media with Septra when the infection is due to** *Haemophilus influenzae* **resistant to ampicillin. To date, there are limited data on the safety of repeated use of Septra in children under two years of age. Septra is not indicated for prophylactic or prolonged administration in otitis media at any age.**

Contraindications: Hypersensitivity to trimethoprim or sulfonamides. Pregnancy and during the nursing period. Infants less than two months of age.

Warnings: SEPTRA SHOULD NOT BE USED IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS.

Clinical studies have documented that patients with Group A β-hemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with Septra than do those patients treated with penicillin as evidenced by failure to eradicate this organism from the tonsillopharyngeal area.

Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias. Experience with trimethoprim alone is much more limited, but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides.

Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBCs are recommended; therapy should be discontinued if a significant reduction in the count of any formed blood element is noted.

Precautions: Use with caution in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur (frequently dose-related). During therapy, maintain adequate fluid intake and perform frequent urinalyses with careful microscopic examination and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Septra. *Blood Dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic Reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal Reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *C.N.S. Reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous Reactions:* Drug fever, chills, and toxic nephrosis with oliguria and anuria. Periarteritis nodosa and L.E. phenomenon have occurred. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia; cross-sensitivity may exist with these agents. In rats, long-term administration of sulfonamides has produced thyroid malignancies.

Dosage and Administration: Not recommended for use in infants less than two months of age.

ACUTE OTITIS MEDIA IN CHILDREN: The recommended dose for children with acute otitis media is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, given in two divided doses every 12 hours for 10 days. The following table is a guideline for the attainment of this dosage using Septra Tablets or Suspension.

Children: Two months of age or older:

Weight		Dose—every 12 hours	
lb	kg	Teaspoonfuls	Tablets
20	9	1 (5 ml)	½
40	18	2 (10 ml)	1
60	27	3 (15 ml)	1½
80	36	4 (20 ml)	2 (or 1 DS tablet)

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual Standard Regimen
15–30	Half of the usual dosage regimen
Below 15	Use Not Recommended

Supplied: SEPTRA TABLETS containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 40, 100, 500 and 1000 tablets; unit dose pack of 100. ORAL SUSPENSION, containing the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole in each teaspoonful (5 ml), cherry flavored—bottle of 450 ml.

Also available in double strength, oval-shaped, pink, scored tablets containing 160 mg trimethoprim and 800 mg sulfamethoxazole—bottles of 60 and unit dose packs of 100.

*Clinical results do not necessarily correspond with *in vitro* data.

†Data on file, Medical Department, Burroughs Wellcome Co.

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V-Cillin K®

Lilly

penicillin V potassium

the most widely prescribed brand of oral penicillin

Tablets—125, 250, and 500 mg.* Oral Solution—125 and 250 mg.*/5 ml.

V-CILLIN K®
penicillin V potassium

Brief Summary. Consult the package literature for prescribing information.

Description: V-Cillin K is the potassium salt of penicillin V. This chemically improved form combines acid stability with immediate solubility and rapid absorption.

Indications: For the treatment of mild to moderately severe pneumococcal respiratory tract infections and mild staphylococcal skin and soft-tissue infections that are sensitive to penicillin G. See the package literature for other indications.

Contraindication: Previous hypersensitivity to penicillin.

Warnings: Serious, occasionally fatal, anaphylactoid reactions have been reported. Some patients with penicillin hypersensitivity have had severe reactions to a cephalosporin; inquire about penicillin, cephalosporin, or other allergies before treatment. If an allergic reaction occurs, discontinue the drug and treat with the usual agents (e.g., epinephrine or other pressor amines, antihistamines, or corticosteroids).

Precautions: Use with caution in individuals with histories of significant allergies and/or asthma. Do not rely on oral administration in patients with severe illness, nausea, vomiting, gastric dilatation, cardiospasm, or intestinal hypermotility. Occasional patients will not absorb therapeutic amounts given orally. In streptococcal infections, treat until the organism is eliminated (minimum of ten days). With prolonged use, nonsusceptible organisms, including fungi, may overgrow; treat superinfection appropriately.

Adverse Reactions: Hypersensitivity, including fatal anaphylaxis. Nausea, vomiting, epigastric distress, diarrhea, and black, hairy tongue. Skin eruptions, urticaria, reactions resembling serum sickness (including chills, edema, arthralgia, prostration), laryngeal edema, fever, and eosinophilia. Infrequent hemolytic anemia, leukopenia, thrombocytopenia, neuropathy, and nephropathy, usually with high doses of parenteral penicillin. [102175]

* Equivalent to penicillin V.

Additional information available to the profession on request.

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Indianapolis, Indiana 46206

This asthmatic isn't worried about his next breath...



he's active
he's effectively maintained on

QUIBRON®

Each capsule or tablespoon (15 ml) elixir contains theophylline (anhydrous) 150 mg and glyceryl guaiacolate (guaifenesin) 90 mg. Elixir: alcohol 15%

- theophylline for effective around-the-clock bronchodilator therapy
- 100% free theophylline

Indications: For the symptomatic relief of bronchospastic conditions such as bronchial asthma, chronic bronchitis, and pulmonary emphysema.

Warnings: Do not administer more frequently than every 6 hours, or within 12 hours after rectal dose of any preparation containing theophylline or aminophylline. Do not give other compounds containing xanthine derivatives concurrently.

Precautions: Use with caution in patients with cardiac disease, hepatic or renal impairment. Concurrent administration with certain antibiotics, i.e. clindamycin, erythromycin, troleandomycin, may result in higher serum levels of theophylline. Plasma prothrombin and factor V may increase, but any clinical effect is likely to be small. Metabolites of guaifenesin may contribute to increased urinary 5-hydroxyindoleacetic acid readings, when determined with nitrosonaphtol reagent. Safe use in pregnancy has not been established. Use in case of pregnancy only when clearly needed.

Adverse Reactions: Theophylline may exert some stimulating effect on the central nervous system. Its administration may cause local irritation of the gastric mucosa, with possible gastric discomfort, nausea, and vomiting. The frequency of adverse reactions is related to the serum theophylline level and is not usually a problem at serum theophylline levels below 20 μg/ml.

How Supplied: Capsules in bottles of 100 and 1000 and unit-dose packs of 100; Elixir in bottles of 1 pint and 1 gallon.

See package insert for complete prescribing information.

Mead Johnson

PHARMACEUTICAL DIVISION

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Marginal Comment

The Nosology of Failure to Thrive

Why Is Psychosocial Deprivation, Its Major Cause, Underdiagnosed?

In his study of the diagnostic aspects of patients with failure to thrive (see p 967 in this issue), Sills points out that only 1.4% of the laboratory studies performed were of positive diagnostic assistance. He found that none of the laboratory studies was of value without a specific clinical indication. This has been suspected by others from anecdotal data.[1] Another important aspect of the investigation by Sills was the finding that half of the children who were being evaluated because of failure to thrive were found to be suffering from environmental deprivation and that this syndrome was the most common cause of failure to thrive in the series reported. The author noted that previous workers have reported higher frequencies of the diagnosis of organic disease, and he attributed this anomaly to a tendency to undervalue the psychosocial investigation of the affected family. This has also been my experience, and it points up the importance of the social history in all cases of failure to thrive.

Indeed, the physician may become so involved in trying to sort out the myriad metabolic, endocrinologic, and genetic possibilities that he unduly postpones an evaluation of psychosocial problems with the parents and social workers. This is understandable since the increased mechanization of clinical problem solving encourages this. It is so much easier to check off a small (or not so small) fortune in laboratory tests on a slip than it is to sit down with a family and have an extended heart-to-heart talk. As the study by Sills implies, if the latter is not done, the diagnosis may well be missed.

What is the reason for this failure of perception of psychosocial disease? One factor inhibiting diagnoses of behavioral conditions may be the historically late entry of such considerations into the arena of differential diagnosis. As a junior faculty member at an eastern university, I was once told by a distinguished professor that I was not to mention again in his presence the possibility that growth failure might be related to environmental deprivation.

Another factor is the ascendancy of biochemical technology in diagnosis, the ultimate elaboration of the early 19th century humoral pathology of Rokitansky. The dazzling success of clinical biochemistry in the diagnosis and management of organic disease in patients has tended to overshadow other modalities of diagnosis. We are preoccupied with the new "toys" of the clinical pathology laboratory, the automated analyzers that measure everything at once—fascinating us like machines in a gumdrop factory. The explosive developments in radiology and nuclear medicine have also contributed to the fever. In other words, we are so overwhelmed by the "improved" perception of disease provided by the biochemical and other technologies that have become available that we may not notice that what is wrong with the patient is *something that they do not measure*! Perhaps we need to reread Bishop Berkeley's[2] discussion of the impact of new technology on our perception of reality.

Somehow, things are not as they should be. We have been assured by Lewis Thomas (*Medical World News*, Jan 24, 1977, p 100) that in the medical science of the future, physicians would be freed of details and they would have time to devote to their patients: "Doctors will no longer be run ragged by the endless technological chores that take up so much of today's day.... And they will then have time to listen, to look after their patients more comprehensively, to worry about their worrying, and to care for them." Thomas was writing about the year 2000 and not about 1978, and hopefully it may be that today is the storm before the calm.

In light of this, it is interesting to look back on the predictions of two other famous men. Karl Marx, laboring over his manuscript in the British Museum, wrote that the highest development of his theory would be the melting away of the apparatus of the socialist state so as to free men for their own pursuits. Bertrand Russell[3] wrote in the 1920s: "But it [the world] will pass away, burned up in the fire of its own hot passions; and from its ashes will spring a new and younger world, full of fresh hope, with the light of morning in its eyes." Three wars later, one wonders. It looks as though predicting is a chancy business. Be that as it may, I wish Lewis Thomas the best of luck with his crystal ball and secretly share his optimism.

The practical lesson to be drawn from all this is unmistakable with respect to the child with failure to thrive. The message is clear from the study by Sills that the psychosocial evaluation of the family should have first priority in the process of differential diagnosis, to avoid missing the identification of the moiety of cases with environmental deprivation.

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Syracuse, NY 13210

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The George Armstrong Award Lecture

Pediatrics

A Perspective on the Present and Future of a Proud Profession

Richard W. Olmsted, MD

This is one of the proudest moments of my life, and I want to thank those who have made it possible for me to be the recipient of the George Armstrong Award. I congratulate the officers and members of the Ambulatory Pediatric Association for their efforts in making the association a leading voice in american pediatrics. I wish briefly to acknowledge my great debt to Dr Grover Powers and Dr Edith Jackson, my teachers at New Haven, Conn, to Dr Waldo Nelson, a stern taskmaster in my early years in academic life, and to Dr Donal Dunphy, my partner in practice, and Dr Joseph B. Bilderback of Oregon, my role models for the complete pediatrician.

I have chosen this title because I believe it is imperative that from time to time each medical specialty undertakes a critical self-assessment to determine how well it is achieving its prime objective, namely, meeting the health needs of the patients whom it serves. This assessment must include an analysis of the adequacy of the educational system, and of the ability of the discipline to respond to the changes in the health needs of its patients, which will inevitably occur. This self-assessment must be based on factual information, painstakingly gathered and intelligently interpreted. It must not be based on theory, inadequate data, or biased perception. Pediatrics has undertaken such a self-assessment. I believe it is important that the perspective gained from it be presented now so that all who are concerned may have a sound base of judgment of the adequacy, or inadequacy, of pediatrics to provide optimum health care to the infants, children, and adolescents in the country now and in the future. It is particularly important that those most responsible for health legislation and health planning at the federal and state levels be provided with these data.

Fortunately, three activities conducted in the past two years have provided a factual base on which such analyses and predictions can be made. These are the Report of the Task Force on Pediatric Education, the Manpower Survey of the American Academy of Pediatrics, and the response to the request by the General Accounting Office of the US government for information on the manpower supply and distribution of each medical specialty.

The Report of the Task Force on Pediatric Education is the result of two years of effort by the first, truly interorganizational body of those concerned with pediatric education at all levels: undergraduate, postgraduate, and continuing education. The organizations comprising the task force are as follows: the American Academy of Pediatrics, the American Board of Pediatrics, the American Pediatric Society, the Society for Pediatric Research, the Ambulatory Pediatric Association, the Association of Medical School Pediatric Department Chairmen, the Society for Adolescent Medicine, the American Academy of Child Psychiatry, and the Association of Teachers of Child Psychiatry.

The task force has been under the able chairmanship of Dr C. Henry Kempe, and has been financially supported by the component societies

From the Department of Pediatrics, University of Colorado Medical School, and the Children's Hospital of Denver.

Reprint requests to Children's Hospital of Denver, 1056 E 19th Ave, Denver, CO 80218 (Dr Olmsted).

and by the Institute for Pediatric Services of the Johnson and Johnson Company, Dr Stephen Sawchuk, director. Two surveys were conducted by the task force to aid in formulation of recommendations. The first was to provide data on pediatricians who had completed their residency training since 1965. This report supplemented the findings of an earlier academy survey. The second concerned the attitudes of mothers toward health care of their infants, children, and adolescents. I believe that the recommendations of the task force, will considerably effect the nature and content of pediatric education.

The Manpower Survey of the American Academy of Pediatrics is a major study that documents not only demographic data related to pediatrics, but of special importance, the attitudes of pediatricians toward the future of their discipline. This survey was conducted under the chairmanship of Dr Robert Burnett, and with the help of Dr Donald Cornely and his staff.

The response of the American Academy of Pediatrics to the "GAO Report" is a less well-known, but extremely important document. It documented for the first time misunderstandings of health planning officials at the federal level regarding the nature and particularly the manpower requirements of the specialty of pediatrics. The report of the task force and the academy will be published soon.

One further introductory comment. The emphasis of this address will be on the present and future status of the private practice system for delivery of pediatric health care. Time is too short to consider the equally important aspects of care delivered through community and public health systems and by those in academic pediatrics. Emphasis will, also, be given to the educational system required to prepare pediatricians to meet adequately the changing health needs of the pediatric population. This discussion will be concerned with the following four subjects: the nature of pediatrics today; the changing health needs of infants, children, and adolescents; the preparation of pediatricians to meet these changing needs; and the future of "Pediatrics."

PEDIATRICS TODAY

There are those who state that there has been controversy in this country as to whether pediatrics should remain a primary care discipline or become subspecialty oriented as has been the trend in internal medicine. I do not believe that this has been a serious controversy because, when historically perceived, pediatrics has always been a primary care discipline in the United States with no serious indication of becoming subspecialty oriented. However, the term "primary care discipline" must not be applied loosely. It must be understood that pediatrics is a comprehensive care specialty and that whereas the majority of pediatric care is primary care, pediatricians by virtue of their training, are capable of and do provide secondary and even tertiary care when indicated. That pediatrics is basically a "primary" care specialty, however, is borne out by recent data that show the following: (1) The vast majority of pediatricians in practice, as well as those in academia, believe that pediatrics is, and should remain, a primary care specialty. (2) Analysis of the content of the practice of pediatricians is clear evidence that their activities are for the most part concerned with primary care. (3) Less than 6% of pediatricians in practice are certified subspecialists or limit their practice to a single subspecialty. There is no evidence to indicate that this percentage is increasing. In fact, it will probably decrease as a result of the recent action of the American Board of Pediatrics to require three core years of pediatrics as a requisite for board eligibility. Finally, nine of ten pediatricians in practice devote more than 75% of their time to "general" pediatrics.

An important finding of both the task force survey and the American Academy of Pediatrics Manpower Survey is that a considerable number of practicing pediatricians either have, or would like to develop, an area of special interest. An area of special interest is to be clearly differentiated from a subspecialty. Individuals who have such interests continue to practice general pediatrics.

Several years ago, there appeared "the dissatisfied pediatrician syndrome." This appelation implied that there was something not quite right with pediatrics. Data from the recent surveys show that far from being dissatisfied, the overwhelming majority of pediatricians find that the practice of pediatrics is intellectually satisfying. Of great importance is the fact that more than 80% of the pediatricians gain professional satisfaction from child health supervision aspects of pediatric practice. These changes in attitudes are undoubtedly related to more efficient systems of practice and more equitable reimbursement mechanisms, but most importantly to the increasing recognition that health supervision and health maintenance activities are the keystones of better health.

These data, and others, which are now available, document that pediatrics is a primary care discipline that is both satisfying and intellectually stimulating. How then is it perceived by medical students and by pediatric residents? Is pediatrics an attractive discipline to young physicians making career choices? The answer is yes. There has been a steady increase in the numbers of US medical school graduates selecting pediatrics as a career. This percentage is now 10. Furthermore, pediatrics has traditionally been, and is remaining, an inviting specialty for women.

It had been considered by some that pediatric residents were electing with increasing frequency to enter academic pediatrics or subspecialties. If that assumption were ever valid, it is no longer so. Data show that the percentage of pediatric residents entering the "general" practice of pediatrics is increasing.

Next, how is pediatrics perceived by the consumers of its care, ie, parents? The task force survey shows that 58% of the mothers are currently using the services of a pediatrician compared with 22% who are using those of a family practitioner and 35% those of general practitioners. In the same survey, pediatricians were clearly rated as the physician best qualified to care for children; 96.8% of the mothers were satisfied with the care received from pediatricians.

The most important consideration of all is the adequacy with which pediatrics is meeting the health needs of children and adolescents today. Although this question cannot be answered accurately, we can, however, make certain observations. The vast majority of practicing pediatricians describe their practices as being "just busy enough," a minority believe that they are "too busy," and an even smaller minority believe that they are "not busy enough." Almost all practicing pediatricians accept new patients, and the waiting time for new patient appointments is remarkably short. Furthermore, the vast majority of pediatricians accept new Medicaid patients. From these data it can be assumed that pediatrics is meeting the health needs of a large segment of the population.

More important, however, is the concern for those not presently receiving care, especially those patients residing in impoverished areas of the inner cities and rural areas. Pediatricians who classify themselves as urban based report that approximately one third of their income is derived from care of that segment of the population that is in the poverty level.

Five percent of practicing pediatricians reside in rural areas where 10% of the nation's children reside. However, these rural pediatricians report themselves as being "least busy." This latter finding indicates that if access to their services can be provided, pediatric physician manpower is likely to be available.

The major barriers to access for health care in the inner cities and remote rural areas are poverty, relatively low levels of education, and lack of appreciation of the importance of health care. These barriers will not be overcome by mere placement of physicians in these areas. Nevertheless, the findings indicate that when the social, cultural, and economic barriers to obtain health care are overcome, the pediatric practice system is available to provide the required health services for this population.

It seems that increasing numbers of pediatricians are entering practice in more remote areas. Many smaller towns in Vermont and Texas, for example, now have pediatricians where formerly there were none. This movement is related partially to the economic reality of supply and demand for pediatric services, and also the recognition of the desirability of living in these areas.

Pediatrics is a dynamic, flexible discipline capable of providing the highest quality of medical care to the largest number of patients having access to its sources. When access is made available for all through more effective health planning, equitable reimbursement mechanisms, and education of those residing in inner cities and isolated rural areas regarding the importance of health care, the specialty of pediatrics will be capable of providing such care. Pediatrics is perceived as a rewarding and intellectually satisfying discipline, and is attracting increasing numbers of US medical school graduates. The public perceives pediatricians as the physicians best qualified to care for children and would prefer care by pediatricians for their children.

The critical self-assessment of a medical discipline must include evaluation of the roles of others in the provision of health care. It is increasingly clear that some health services for children and adolescents can be provided by nonpediatricians. Some medical specialties have turned to the disciplines of physician assistants, nurse midwives, and others. Data now indicate that the pediatric nurse associate (PNA) can play an important role. The academy's manpower survey indicates that under ideal circumstances, the majority of pediatricians would choose to employ a PNA in their practice. Pediatric nurse associates may increase not only the quantity but the quality of services provided, in such areas as health supervision, health maintenance, and counseling. Collaboration with a PNA will enable the pediatrician to devote more time to complex, time consuming problems. It must be clear, however, that if PNAs are to obtain their rightful place in provision of pediatric services, there must be appropriate medical input into their education and certification.

CHANGING HEALTH NEEDS OF INFANTS, CHILDREN, AND ADOLESCENTS

The health needs of children and adolescents are changing. There is an increasing incidence of problems of a "biosocial" and developmental nature. The term biosocial is used here to denote those problems that are induced or complicated by social and environmental factors. These problems have been referred to by other terms such as psychosocial and behavioral. With increasing frequency, the practicing pediatrician is being called on to aid parents and children in coping with the challenges of modern society.

The most dramatic change in pediatric practice is the increased demand for school and educationally related problems, and for a wide variety of behavioral problems: counseling of parents and children in situations of divorce and for those in one parent families is requiring increasing amounts of a pediatrician's time. The appalling increase in child abuse and neglect, and now the emergence of sexual abuse, means that pediatricians are increasingly assuming the role of child advocate in areas such as juvenile justice, custody, and foster home placement. The need for counseling in problems relating to sexuality and teenage pregnancy, substance abuse, depression and conversion states, alienation, and suicide attempts is also increasing. Indeed, suicide now ranks as the second leading cause of death in the adolescent-age period.

As children with handicaps and those with chronic illnesses live longer, due to medical advances in their care, new health needs for them and for their families present themselves. Changes in pediatric education will be required to prepare the pediatricians of the future to meet these changing health needs, and comparable changes in pediatric practice are anticipated.

PEDIATRIC EDUCATION

Preparation of pediatricians to meet the health needs of their future patients will necessitate changes in training programs. Some of these changes have already occurred.

The recent action by the American Board of Pediatrics to require three core years of pediatric training for eligibility for board examination is one such change. It is recognized by the board that the body of knowledge in pediatrics is now so broad that it cannot be mastered in less than three years of postgraduate training. This requirement will essentially eliminate the obtaining of credit for three years through the route of two core years, plus two years of subspecialty training. It will also eliminate the pyramid system of pediatric residency training. Hereafter, program directors must guarantee entering residents three years of training. Within the three core years, time will be available for teaching the currently underemphasized areas of pediatrics. This action of the board will also reduce or eliminate the offering of two year subspecialty fellowships to individuals who are not seriously concerned with an academic or research career.

The Task Force on Pediatric Education recognizes three areas presently underemphasized that will require change in pediatric education; the management of biosocial, developmental, and educational problems; adolescent medicine; and the care of children with handicaps and those with chronic illness. This will necessitate additional faculty in the behavioral sciences, and a closer collaboration with other departments of medical schools, particularly child psychiatry. Faculty who are knowledgeable in the field of adolescent medicine will also be needed.

Now that recertification has become a reality, programs of continuing education will have "teeth" in them. The program for continuing education leading to recertification, developed jointly by the American Board of Pediatrics and the academy, will provide a basic curriculum from which a plan of continuing study can be developed. Pediatric departments should undertake the responsibility for provision of continuing education in the true spirit of the university.

THE FUTURE OF PEDIATRICS

The history of pediatrics is replete with attempts to predict the future of the discipline. Not all of these predictions have proved valid. However, through the efforts of the Task Force on Pediatric Education, the academy, and others, I believe we now have adequate information with which to predict at least some aspects of the future of pediatrics. The nature of pediatrics in the future will depend on the ability of the discipline to meet the changing health needs of the patients.

One predicts a care system that will be adequate to meet the health needs of infants, children, and adolescents providing that the percentage of US medical school graduates who choose pediatrics as a career, now 10%, continues.

It is anticipated that family physicians will continue to supply certain amounts of health care to the pediatric population. They will likely find, however, as the population ages, that increasing amounts of the family physician's time will be devoted to care of the elderly. There is, also, serious concern on the part of many regarding the adequacy of family practice training programs to prepare the physician adequately to care for children. Unless their training programs are considerably strengthened in regard to pediatrics, it is not likely that family physicians will be capable, or desirous of, providing a large segment of care to children. The task force survey of mothers indicates that when financial and other barriers of access to care are lessened, the public will elect to have care for children and adolescents delivered by those best qualified to provide such care, namely pediatricians. At the present time, only about 7% of pediatricians indicate that their practice has been "adversely" affected by the emergence of family physicians.

Similar comments may be made in regard to the amount of care to be given to adolescents by internists. There is little indication at the present time of desire on the part of internists to become involved to any serious degree with care of adolescents. As with family physicians, increasing amounts of the internists' time will likely be spent in caring for the elderly, and it is unlikely that they will provide much more care for adolescents in the future than they do at the present.

One predicts that the large majority of pediatricians will be practicing in groups together with one or more PNAs. Many of these pediatricians will have an area of special interest in addition to general pediatrics. The development of areas of special interest may have important implications for the medical care system. Pediatricians with areas of special interest continue to practice general pediatrics. However, some percentage of their time may be devoted to provision of services that fall within their area of special interest. This may take the form of intragroup consultation and referral and participation in community programs, eg, cardiac screening programs, care of handicapped children, or spending of portions of time with certain patients within his own practice, for example, children with school-related problems or adolescents. The ability to provide intragroup consultations may lessen the need for referral of patients to tertiary care centers, referrals which are costly and which may fragment care. It is of importance that the special interest areas that pediatricians have, or would wish to develop, are highly concentrated in the biosocial, educational, and counseling areas of pediatrics, precisely the areas which the task force considers to rank high among the unmet health needs of children and adolescents.

It is predicted that increased amounts of physician time per patient will be required because of the complexity of the problems. This is particularly true of the management of biosocial, developmental, behavioral, and educationally related problems and in the care of the adolescent. The practicing pediatrician of today sees an average of 27 patients a day in his office. It is likely that if he is to participate in the management of children with more complex problems, he may effectively be able to care for approximately 20 patients a day. The health needs of adolescents today are being inadequately met. Pediatrics must take on the full responsibility for improving the health care of this

segment of the population.

To meet these challenges, changes will be required not only in deployment of pediatrician's time and activities, but in reimbursement for his services. It is predicted that a certain amount of a pediatrician's current activities will be delegated to training nonphysician personnel. This is particularly true in the area of health supervision, anticipatory guidance, and management of minor illness. The individuals most capable of assuming these responsibilities at the present time are the PNAs. However, the overall acceptance of the PNA in the future will depend on many factors, the most important of which will be the demand of the marketplace and the quality of the training programs for PNAs and their graduates.

Of greatest importance will be the development of adequate reimbursement mechanisms for management of patients and, particularly, for those problems of biosocial, developmental, and educational nature, and for counseling. Less than 35% of the families have insurance covering office visits. Since these policies are generally procedure oriented, counseling and psychosocial services are usually excluded.

In the recent survey of the Task Force on Pediatric Education, pediatricians were asked about provision of services, such as counseling or management of learning disorders and other biosocial problems. Eighty percent replied that they did provide such services. Of these, 45% reported that they were not reimbursed in proportion to time spent in counseling. Less than 5% said that they were always reimbursed in proportion to their time. The most common method of reimbursement was direct payment by the parent or guardian.

The Task Force on Pediatric Education calls attention to the recommendation of the Professional Affairs Committee of the National Association of Blue Shield plans that states that insurance coverage of health evaluations for children is desirable, particularly since medical treatment is often more effective in this age group and since children are less able than adults to identify and act on their health problems.

Federal regulations for support of training of pediatricians and internists in primary care, require that residents have experience with problems of psychosocial nature. Hence, ways must be found to adequately reimburse the physician for these services, and as well as for those rendered in managing biosocial problems.

Clearly, pediatrics is demonstrating its current strength. It is demonstrating, also, that as demand for pediatric services increases, the specialty will probably be able to provide the manpower required. Pediatrics is demonstrating its flexibility to meet changing demands through its leadership in the development of the PNA concept. It has identified the important fact that the health needs of the population are changing, and there is every indication that its educational system will begin to provide the types of preparation of pediatricians that will be required to meet these changing needs.

George Armstrong has been called the father of pediatrics. In review of his life, one senses that he must have been a proud man. Despite serious financial problems which forced him to drop out of medical school before receiving his MD degree, he did receive it several years later. He must have taken great pride in that accomplishment. The dispensary he founded was supported mainly from his limited earnings. He must have been terribly proud of his dispensary. One reads that George Armstrong's later years were filled with tragedy, with trouble with creditors (probably as a result of his efforts to support the dispensary) and he may actually have been imprisoned for nonpayment of a debt. Later, he was felled by a stroke, and at the age of 69 years, he died in obscurity. Despite these unfortunate events, the pride in what he had given to children must have remained as a high-guiding beacon.

As I think of George Armstrong as a proud man, so do I think of pediatrics as a proud profession. Proud of its monumental contributions to the health and welfare of all children. Proud of its willingness to undertake this critical self-analysis and to demonstrate its acceptance of the challenge of change that will be required to meet the health needs of its patients in the future. In accepting these challenges, pediatrics has again led the way for all other medical disciplines.

Articles

Failure to Thrive

The Role of Clinical and Laboratory Evaluation

Richard H. Sills, MD

• **One hundred eighty-five patients hospitalized for evaluation of failure to thrive were reviewed retrospectively. Eighteen percent had proven organic etiologies. The specific organic diagnosis was strongly suggested by the history and physical examination in all of these patients. Fifty percent of the patients were failing to thrive on the basis of environmental deprivation. Only 1.4% of the laboratory studies performed were of positive diagnostic assistance. No study was of positive value without a specific indication from the clinical evaluation. The history and physical examination are the most valuable tools in the evaluation of failure to thrive. Laboratory investigations are rarely helpful without a specific indication from the clinical evaluation.**

(*Am J Dis Child* 132:967-969, 1978)

The evaluation of a child who fails to thrive is a common pediatric problem. Although the literature contains numerous discussions of the differential diagnosis,[1-8] a systematic analysis of the diagnostic approach to this entity has received little attention.[9] A large experience with failure to thrive is reviewed here in order to better define the evaluation of this problem.

SUBJECTS AND METHODS

Charts of all patients admitted to the Children's Hospital of Buffalo (NY) for a diagnostic evaluation of failure to thrive during a recent 34-month period were reviewed. These patients were accepted into the study if they fulfilled the following criteria: (1) They were less than 3 years of age. (2) Their weight was less than the third percentile on the Boston Children's Hospital Medical Center Anthropometric Charts, or their weight had shown a decrease greater than two major percentiles (eg, from above the 90th to the 50th percentile, defining the major percentiles as 97th, 90th, 75th, 50th, 25th, tenth, and third). All ages were corrected for gestational age.

Charts were reviewed for the value of history, physical examination, and laboratory data in establishing a diagnosis.

RESULTS

A total of 185 patients were identified who fulfilled the above criteria. They represented 1.4% of the medical admissions to the Children's Hospital during the study period.

The patients were divided into three general diagnostic categories (Table 1): (1) Nonorganic etiology (58% of patients). The great majority (92/105) of this group failed to thrive on the basis of environmental deprivation. This was established on the basis of substantial and persistent weight gain on removal from the home environment, a history of social problems in the family, and lack of evidence of organic disease. Other causes consisted of simple problems in feeding techniques, rumination, constitutional growth delay, and genetic short stature. (2) Organic etiology (18% of patients). Thirty-four of 185 patients had proved organic etiologies for their failure to thrive. Table 2 lists the specific organic diseases in these patients. Gastrointestinal and central nervous system disorders were the most common, accounting respectively for 40% and 20% of the organic etiologies. (3) Undetermined etiology (24% of patients). No definitive diagnosis was established in this group. The clinical and laboratory examinations had not provided any clue suggesting an organic etiology. An attempt was made to obtain more recent information concerning growth from private or clinic physicians in order to exclude overlooked cases of organic disease. Follow-up was available in 14 patients; 13 were growing at a constant rate paralleling a growth curve at or just below the third percentile.

Table 1.—Patients With Failure to Thrive

	No. (%) of Patients (N = 185)
Nonorganic etiology	106 (58)
Environmental deprivation	92 (50)
Simple feeding problem	5 (3)
Rumination	5 (3)
Constitutional and familial	4 (2)
Organic etiology	34 (18)
Undetermined etiology	45 (24)

From the Department of Pediatrics, Children's Hospital of Buffalo (NY).

Reprints not available.

Table 2.—Organic Causes of Failure to Thrive	
	No. of Cases
Gastrointestinal	14
Chronic severe gastroenteritis of unknown cause	4
Pyloric stenosis	3
Malrotation	1
Chronic diarrhea with enteropathogenic *Escherichia coli*	1
Hirschsprung's disease	1
Chalasia	1
Pancreatic insufficiency, idiopathic	1
Probable milk allergy	1
Probable celiac disease	1
Central nervous system	7
Severe mental retardation and cerebral palsy	5
Severe mental retardation and multiple congenital abnormalities	2
Pulmonary	3
Recurrent pneumonia	2
Recurrent aspiration pneumonia and nasopharyngeal reflux	1
Cardiovascular	2
Coarctation and myocardiopathy	1
Multiple congenital abnormalities and atrial septal defect and patent ductus arteriosus	1
Endocrine	2
Hypothyroidism	2
Metabolic	2
Mental retardation and failure to thrive secondary to maternal phenylketonuria	2
Chromosomal	1
Turner's syndrome	1
Immunologic	1
Increased IgE, eczema, and immune deficiency	1
Muscular	1
Muscular dystrophy	1
Other	1
Presacral teratoma	1

Table 3.—Distribution of Useful Laboratory Data		
Type of Study*	No. of Studies Done	No. (%) of Studies That Assisted Diagnosis
Hematologic (CBC count, ESR, coagulation studies, etc)	363	1 (0.3)
Urinary (analysis, VMA, amino acids, etc)	227	0 (0)
Chemistry (electrolytes, creatinine, enzymes, blood gases, etc)	1,080	8 (0.7)
Radiologic (all roentgenograms and radioisotope scans)	437	21 (4.8)
Cultures (blood, urine, stool, ova, and parasites)	213	1 (0.5)
Stool studies (pH, reducing substances, fat, etc)	43	0 (0)
Endocrine (thyroid studies, etc)	64	2 (3.1)
Serologic (antibody titers, immunoglobulins, etc)	67	1 (1.5)
Sweat test	63	0 (0)
Chromosomal studies	13	0 (0)
All other studies	37	2 (5.4)
Total	**2,607**	**36 (1.4)**

*Laboratory tests considered as single studies were urinalysis (including pH, specific gravity, reducing substances, ketones, protein, blood, sediment examination), CBC count (including hemoglobin, hematocrit, RBC and WBC counts, RBC indices, differential cell count, and examination of smear), serum electrolytes (Na, K, Cl, CO_2 content), immunoglobulins (IgA, M, G), all coagulation studies, and all viral titers.

In the patients with nonorganic causes for their failure to thrive, a thorough history alone usually provided the clue to the diagnosis. In patients with organic etiologies, the history or physical examination or both helped suggest the underlying etiology in all 34 patients:

	No. of Cases
History alone useful	17
Physical examination alone useful	1
History and physical examination useful	16
Laboratory studies useful without suggestion from clinical examination	0

In the entire series of 185 patients, all the cases of organic disease were at least strongly suggested by the clinical examination.

A total of 2,607 laboratory tests were performed in the 185 patients, an average of 14 tests per patient. There were 14.1 tests per patient in the organic etiology category vs 13.9 in the nonorganic etiology category.

When all of the 2,607 studies performed in these 185 patients are considered, only ten (0.4%) served to establish a diagnosis, while an additional 1% were able to support a diagnosis. In summary, only 1.4% (36/2,607) of these studies were of positive diagnostic assistance.

Table 3 details the value of each general category of laboratory studies in our patients. The most useful individual studies were the upper gastrointestinal series (nine patients), the chest roentgenogram (six patients) and the barium enema (three patients). However, in all these instances, a complete history and physical examination provided a specific indication for the radiologic studies. Of the 36 studies that were of positive value, all were specifically indicated by the clinical examination.

COMMENT

This study demonstrates that organic disease is responsible for only a small percentage of infants and children who fail to thrive. It also illustrates that an organic etiology of failure to thrive can be ascertained on the

basis of a careful history and physical examination.

Eighteen percent of our patients had organic causes for their failure to thrive, compared to a range of 47% to 68% reported in the literature.[1,2,9] Ambuel and Harris[9] reported a 68% incidence of organic disease in 100 cases, but their selection process included previously recognized cases of organic disease. Hannaway[1] reported a 49% incidence in 100 patients, but the selection criteria were not clearly specified. Riley et al,[2] using selection criteria similar to that used in this study, reported a 47% incidence in 83 cases. The variance is difficult to explain. A bias that may exist in many studies is the tendency to look for the organic causes of failure to thrive, while searching with less diligence for cases of environmental deprivation.

A thorough and tactfully solicited psychosocial history will often suggest the diagnosis of environmental deprivation from the outset. In our patients, the social history was frequently markedly deficient. The correct diagnosis was often recognized only when the child began to gain weight in the hospital. It appeared that parents usually carefully avoided discussing psychosocial problems. A suggested diagnosis of environmental deprivation on the basis of the history (with or without adequate caloric intake) is confirmed by the child's weight gain in the hospital environment.

The study also disclosed a 24% incidence of failure to thrive in which no diagnosis was established. In their study of 83 patients, Riley et al[2] had a comparable 20% incidence of undiagnosed patients. The additional follow-up available in 14 of 45 patients showed that 13 of 14 were growing at a rate paralleling a growth curve at or just below the third percentile. This suggests that an organic etiology was unlikely in most patients in this group. Constitutional growth delay or genetic short stature are likely explanations for this borderline growth pattern, but environmental deprivation may also occur in this fashion.

One of the primary purposes of this study was to examine the value of laboratory investigations in the evaluation of failure to thrive. The only previous examination of such data was by Ambuel and Harris.[9] They found that the history and physical examination alone furnished "leads" in 91% of their patients and established a diagnosis in 32%. As noted above, the study had a definite bias toward organic causes. The current study clearly demonstrates the primary role of the history and physical examination in the evaluation of failure to thrive. The clinical examination was able to suggest the final diagnosis in all 34 patients in whom a diagnosis of organic disease could be established. Of 2,607 laboratory studies performed in 185 patients, none were useful without a specific indication from the history and physical examination. It is impossible to evaluate the value of negative laboratory studies in a retrospective study.

My conclusion is certainly not that the laboratory examination will never be useful without a clinical indication. I do, however, suggest that the patient whose clinical examination does not suggest an organic etiology is unlikely to benefit from an extensive laboratory evaluation unless the much more likely nonorganic causes are ruled out first.

Although the retrospective nature of this study makes the data more difficult to interpret, certain conclusions are clear:

1. Organic disease is the underlying cause of failure to thrive in a minority of patients. A specific organic cause, when present, is strongly suggested by a complete history and physical examination in the vast majority of parents. Appropriate laboratory studies can then be obtained to confirm this specific clinical impression.

2. Constitutional growth delay or genetic short stature are most likely when the clinical evaluation is not suggestive of organic disease or environmental deprivation and the child's growth curves are close to and parallel to the third percentile. Family history should be helpful. A period of outpatient observation is all that is required unless the child's growth exhibits deterioration.

3. Environmental deprivation is the most common cause of failure to thrive. A detailed, carefully elicited psychosocial history is essential in establishing this diagnosis. Parents of a child who is failing to thrive on the basis of environmental deprivation are usually reluctant to discuss their severe family problems. An expression of compassion and concern for the parents and their problems, as well as for the child, often leads to a more productive and less guarded social history. This process may require several sessions with either or both parents.

If the clinical evaluation is not helpful or if it suggests environmental deprivation, hospitalization is indicated. A new environment is provided that is conducive to growth, as well as an optimal diet and social interaction with the staff. An extensive laboratory evaluation is *not* indicated. If the etiology is environmental, definite weight gain will ensue in most cases within 10 to 14 days.[10]

Elliot F. Ellis, MD; Janifer M. Judisch, MD; Margaret H. MacGillivrey, MD; Frank A. Oski, MD; James A. Stockman III, MD; and Mary L. Voorhess, MD, reviewed this article and provided suggestions.

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Sex Liability to Single Structural Defects

J. Fernando P. Arena, MD, PhD, David W. Smith, MD

• **Forty-two of 52 single, localized defects of morphogenesis showed a nonrandom predeliction to one sex. For some of these malformations, the sex liability may be explained on the basis of normal anatomic or hormonal differences between the sexes. For example, the male excess of "prune belly" or triad syndrome is considered due to the fact that most cases are secondary to obstruction in the penile urethra, and the male excess of pyloric stenosis is hypothesized as being secondary to the muscle hypertrophying effect of testosterone in the male neonate. The sex differences for most of the defects suggest that genes on the X and/or Y chromosome exert a role in morphogenesis that extends well beyond the development of sex-related structures.**

(*Am J Dis Child* 132:970-972, 1978)

Past studies have noted a difference in the sex incidence of single malformations in man.[1] The largest study was that of Hay[2] that dealt with ten such defects. The purpose of the present study was to evaluate *all* single, localized structural defects for which adequate data could be obtained to calculate sex ratios and determine the relevance of the findings.

METHODS

The literature was reviewed regarding the incidence of single, localized, structural defects in each sex, and the sex ratio was tested by a χ^2 test to verify any substantial differences from expectation. The study includes only malformations and malformation complexes, the later representing the consequence of a single, localized structural defect plus its derived additional defects.[3] An attempt was made to only use instances in which the single malformation or malformation complex was present in an otherwise normal individual, thus excluding syndromes of malformation.

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RESULTS

Adequate data was available for a total of 52 different malformations or malformation complexes as given in the Table. For 81% of them, the sex ratio differed greatly from expectation. There was a male preponderance in sex ratio for 50% of the studied defects and a female excess for 31% of them. The degree of sex preponderance ranges from abdominal muscle deficiency malformation complex that is almost 20 times as common in males, to dislocation of the hip that is almost five times as common in females. Categorization of the defects by organ system or anatomical region showed a relative male excess for all, except for defects of the nervous system.

COMMENT

Genetically determined XX vs XY anatomical differences among individuals may explain the sex preponderance for certain of these defects of morphogenesis. For example, the reason for the huge excess of hypospadias in the XY vs XX individual is so obvious that it was not included in this study. We believe that the great excess of the so-called "prune belly" syndrome in the male may be explained on a similar basis, relating to a urogenital malformation that is usually dependent on male-type genital development for its presence. One of us (D.W.S.) has done research that strongly implies that the prune belly is a nonspecific feature that is most commonly the consequence of urethral obstruction at the prostatic urethra, a defect that would generally only happen in the male. The abdominal findings are considered secondary to early urethral obstruction that leads to gross bladder distention with thinning out of the abdominal wall and its musculature. This is often lethal in early fetal life unless the bladder ruptures via the urachus or urethra to decompress the expanding bladder mass and yield the wrinkled prune belly by birth. The excess of inguinal hernia in the male may be related to the descent of the testicles, which would enhance the likelihood of the inguinal canals remaining patent in the male vs the female.

Physiological differences, such as sex hormonal differences during fetal life, can perhaps explain the sex preponderance of some structural defects in the male vs the female fetus. The major recognized sex hormonal difference during fetal life is testosterone,[4-6] which is produced by the male from 8 weeks of fetal life until several months after birth, whereas fetal estrogen values do not differ appreciably between the sexes.[7] The effects of testosterone on muscle might explain the excess frequency of hypertrophy of the pyloric muscle leading to pyloric stenosis in the male. Testosterone-induced hypertrophy of muscle has been shown both in vivo and in vitro.[8-11] This hypothesis has received some unexpected support from a study by one of us (D.W.S.) on the short-term use of systemic testosterone therapy to enlarge an unduly small penis toward normal size during infancy.[12] To our knowledge, the experience to date includes three XY males with micropenis in whom intramuscular testosterone therapy (25 mg, intramuscularly every three weeks for three months) was started during the first three postnatal weeks of life. All were testosterone responsive and showed penile growth. In two of these three boys, pyloric stenosis developed that required surgical intervention; one boy received the first injection of testosterone at 1 week of age and began projectile vomiting five days later while the other boy was begun on treatment at three weeks of age and commenced vomiting eight days later. These findings are compatible with the hypothesis that a higher dose of testosterone might enhance muscular hypertrophy and increase the liability toward pyloric stenosis in the neonate. Though we would view testosterone as

Sex Preponderance of Single Structural Defects of Morphogenesis					
Source	Malformations and Malformation Complexes	Total No. of Occurrences	M Excess	F Excess	P
Nervous system					
Stevenson et al[15]	Anencephaly	381	...	1.9	<.001
Roach et al[16]	Alobar holoprosencephaly	19	...	2.8	<.05
Lorber,[17] Mealey et al[18]	Occipital encephalocele	55	...	2.7	<.001
Lorber,[17] Mealey et al[18]	Encephalocele other than occipital	42	...	...	...
Carter and Evans[19]	Meningomyelocele (spina bifida)	631	...	1.3	<.01
Craniofacial					
Shillito and Matson[20]	Craniosynostosis, sagittal only	289	3.6	...	<.001
Shillito and Matson[20]	Craniosynostosis, coronal only	127	...	1.5	<.05
Meskin et al[21]	Cleft uvula	115	...	...	...
Hay[2]	Cleft palate	5,476	...	1.2	<.001
Hay[2]	Cleft lip ± cleft palate	12,316	1.9	...	<.001
Cardiovascular					
Fontana and Edwards,[22] Selzer[23]	Ventricular septal defect	150	...	...	...
Fontana and Edwards,[22] Abbott[24]	Transposition of great vessels	58	2.6	...	<.001
Fontana and Edwards,[22] Abbott,[24] Brinton and Campbell[25]	Tetralogy of Fallot	153	1.4	...	<.05
Fontana and Edwards,[22] Roesler[26]	Atrial septal defect	91	...	1.6	<.05
Fontana and Edwards,[22] Abbott[24]	Patent ductus arteriosus	115	...	1.9	<.01
Fontana and Edwards,[22] Abbott,[24] Morino et al[27]	Coarctation of aorta	354	2.3	...	<.001
Fontana and Edwards[22]	Pulmonary stenosis	126	...	...	...
Fontana and Edwards[22]	Truncus arteriosus	78	1.6	...	<.05
Fontana and Edwards[22]	Persistent common atrioventricular canal	54	...	...	...
Fontana and Edwards[22]	Cor biloculare	63	...	...	...
Fontana and Edwards[22]	Cor triloculare biatrium	64	2.4	...	<.01
Roberts[28]	Bicuspid aortic valve	85	2.5	...	<.001
Braunwald et al[29]	Aortic valve stenosis	100	4.0	...	<.001
Fontana and Edwards[22]	Aortic valve atresia	68	3.2	...	<.001
Child and Dennis[30]	Hypoplastic left heart	52	...	2.1	<.05
Fontana and Edwards[22]	Total anomalous pulmonary venous connection	49	...	...	...
Intestinal					
Hay[2]	Esophageal atresia with or without fistula	1,148	1.4	...	<.001
Bartels,[31] Kammerer,[32] Kremer et al[33]	Stomach duplication	63	...	2.2	<.001
Myrianthopoulos and Chung[34]	Pyloric stenosis	61	4.1	...	<.001
Gross[35]	Meckel's diverticulum	159	3.3	...	<.001
Kiesewetter et al[36]	Anal atresia with or without fistula	146	1.8	...	<.001
Skeletal					
Gray et al[37]	Klippel-Feil anomaly	390	...	...	...
Riseborough and Wynne-Davies[38]	Idiopathic scoliosis	208	...	4.3	<.001
Myrianthopoulos and Chung[34]	Pectus excavatum	60	3.0	...	<.001
Ireland et al[39]	Poland malformation complex	43	2.6	...	<.01
Stevenson et al[15]	Polydactyly preaxial	60	...	...	...
Stevenson et al[15]	Polydactyly postaxial	157	...	...	...
Hay[2]	Syndactyly (hand)	2,260	1.8	...	<.001
Myrianthopoulos and Chung[34]	Dislocation of the hip	67	...	4.6	<.001
Palmer et al[40]	Talipes equinovarus	240	2.1	...	<.001
Hay[2]	Talipes calcaneovalgus	129	...	1.9	<.001
Myrianthopoulos and Chung[34]	Metatarsus adductus	287	1.4	...	<.01
Others					
Johnson et al[41]	Diaphragmatic hernia	62	1.9	...	<.02
Hay[2]	Umbilical hernia	1,594	...	1.7	<.001
Myrianthopoulos and Chung[34]	Inguinal hernia	229	7.8	...	<.001
Welch and Kearney[42]	Urethral obstruction malformation complex, "prune belly" syndrome	245	19.4	...	<.001
Hay[2]	Omphalocele	1,552	1.2	...	<.001
Gross,[43] Harvard and Thompson,[44] Higgins,[45] Uson et al[46]	Exstrophy of bladder	518	2.3	...	<.001
Potter[47]	Bilateral renal agenesis	50	2.6	...	<.01
Kampmeier[48]	Sirenomelia	52	2.7	...	<.001
Myrianthopoulos and Chung[34]	Strawberry/port-wine hemangioma	706	...	1.5	<.001
Myrianthopoulos and Chung[34]	Cavernous hemangioma	192	...	1.8	<.001

simply one factor in the liability to development of pyloric stenosis, it might be the major factor responsible for the male sex predilection.

The impact of testosterone on the strength of connective tissue[13] merits consideration as an explanation of the lower frequency of dislocation of the hip, talipes calcaneovalgus, and scoliosis in the male, these defects being more likely to occur with relative connective tissue laxity in the female.

These explanations of an anatomical basis, such as differences in urogenital morphogenesis, or a physiologic basis such as sex hormonal differences, account for all five of the defects for which sex preponderance is more than fourfold excess in one sex. Most of the remaining defects with a sex preponderance must have been engendered before there was a fetal urogenital difference or sex hormone difference, prior to 8 fetal weeks of life, and hence would not be explained in these ways. For some of these early defects in morphogenesis, the sex difference by birth might relate to selective, early fetal mortality. Such a possibility would be especially germane for some of the defects that have a high early lethality such as anancephaly and holoprosencephaly.[14] Beyond these considerations, the observed sex differences for most of the studied defects imply that the genetic background of XX vs XY plays a relevant role in the liability to most single defects of morphogenesis. Our obvious inference is that the genes on the X and/or Y chromosome exert a role in morphogenesis, a role beyond the development of sex-related structures.

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25-Hydroxycholecalciferol for Early Neonatal Hypocalcemia

Occurrence in Premature Newborns

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• **Oral 25-hydroxycholecalciferol ($25OHD_3$) has been used to prevent early neonatal hypocalcemia. Thirty premature neonates were studied prospectively from birth: 22 premature infants constituted a control group, and eight were treated orally with $25OHD_3$ (2 μg/kg/day) for five days beginning within the first 12 hours of life. Eleven of the 22 premature infants in the control group became hypocalcemic, with serum ionized calcium (Ca^{++}) level less than 3.0 mg/dl and total calcium (Ca_T) level less than 7.0 mg/dl on day 2 of life. Only one of the eight premature infants treated with $25OHD_3$ became hypocalcemic. In treated neonates, serum 25-hydroxyvitamin D, as well as serum Ca^{++} and Ca_T levels, increased during the first five days of life and were considerably greater than levels in control neonates. No untoward effects of this treatment were observed.**

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The pathological decrease in serum calcium level that occurs in the first days of life in the premature neonate is the result of a complex interaction of several factors. Varying causes have been suggested for early neonatal hypocalcemia, including functional hypoparathyroidism,[1,2] end-organ unresponsiveness to parathyroid hormone (PTH),[3] hypercalcitoninemia,[4,5] abnormalities in vitamin D metabolism,[6-8] hyperphosphatemia,[9] hypomagnesemia,[1,9] and decreased calcium intake and absorption.[10]

Maternal serum level of ionized calcium (Ca^{++}) decreases during pregnancy[11,12] and is associated with an increase in maternal serum PTH level.[13] There is an active placental pump of calcium from the maternal to fetal circulation, resulting in a relatively increased serum calcium level in the fetus.[14] Fetal PTH level is usually low or undetectable,[1,2] and PTH probably does not cross the placenta.[15] Though neonatal serum PTH level was reported not to increase in response to a decrease in serum Ca^{++} during the first three days of life,[1,2] recent reports have shown that the serum concentration of PTH does increase in premature neonates during the first 48 hours of life as serum Ca^{++} decreases.[5,16] This work in humans confirmed our previously reported findings in nonhuman primates.[15] However, the increase in serum PTH level in these premature infants is not associated with rapid restitution to normocalcemia, suggesting end-organ unresponsiveness to the hormone or involvement of other factors that impede or control the actions of PTH.

Vitamin D undergoes two enzymatic hydroxylations to reach full biological activity. The first metabolic step occurs in the liver, where vitamin D is converted to 25-hydroxyvitamin D (25OHD).[17] This 25OHD then undergoes a second hydroxylation in the kidney to produce the hormonal form of the vitamin, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$).[18] Maternal serum levels of vitamin D and its metabolites are determined, as they are in the nonpregnant state, by exposure of the skin to ultraviolet irradiation and dietary intake of vitamin D.

It has been reported that serum levels of 25OHD decrease during gestation because of increased metabolic breakdown or decreased formation of 25OHD.[19] This may be due to effects of maternal corticosteroids on hepatic microsomal enzyme systems relating to vitamin D metabolism. Maternal and fetal serum levels of 25OHD correlate, which suggests that 25OHD crosses the placenta.[6,20] Previously, we found low serum levels of 25OHD in 11 of 15 premature neonates with hypocalcemia.[6] Insufficient serum 25OHD level might result in decreased formation of $1,25(OH)_2D$, resulting in decreased gastrointestinal absorption of calcium and inability of $1,25(OH)_2D$ and PTH to mobilize calcium from bone.

Another report has suggested that there is no correlation between serum 25OHD level and early neonatal hypocalcemia in premature infants.[5] However, premature infants have been reported to be unable to increase serum 25OHD levels in response to oral or intravenous vitamin D.[21] This is presumably due to decreased 25-

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hydroxylase activity in the liver of these premature neonates.

A simple, unifying explanation of the pathophysiology of early neonatal hypocalcemia is not available at the present time. This derangement in calcium homeostasis is the result of a complex interaction of many variables. However, prevention and treatment of this disorder in premature neonates could be directed toward increasing gastrointestinal absorption of calcium and increasing PTH effectiveness at bone by providing adequate substrate for the physiologic formation of appropriate quantities of $1,25(OH)_2D$.

This study was undertaken to (1) evaluate prospectively the relationship of serum 25OHD level and early neonatal hypocalcemia in premature infants, and (2) study the effectiveness of oral 25-hydroxycholecalciferol ($25OHD_3$), beginning from the first day of life, in preventing early neonatal hypocalcemia.

PATIENTS AND METHODS

A total of 30 premature neonates were studied during the two-year period from August 1975 to July 1977. The infants were born in the hospital in which they were studied. The population is urban poor of black and Hispanic origin. Informed consent was obtained from parents in accordance with institutional and governmental regulations after the nature of the study had been fully explained.

An infant was included for study only if gestational age was 36 weeks or less and weight was 1,800 g or less. Gestational age was determined by maternal dates and neurologic and physical criteria. Neonates were resuscitated as necessary and cared for in a special care nursery. Feedings were begun whenever possible within the first 12 hours of life and supplemented with intravenous fluids when the neonates were unable to take an adequate volume orally. Oxygen and respiratory assistance were administered as necessary to maintain adequate ventilation and oxygenation. Serial measurements of serum bilirubin were performed and phototherapy was instituted when deemed appropriate by the attending physician.

Maternal sera were obtained on the day of delivery for serum levels of total calcium (Ca_T), magnesium (Mg), inorganic phosphate (P), and 25OHD. Neonatal sera were obtained on days 1, 2, 3, 5, and 14 of life. Serum levels of Ca^{++}, Ca_T, and Mg were measured on each sample. Serum 25OHD level was measured on days 1, 5, and 14. Serum P was measured on day 1 and whenever possible on subsequent samples.

A total of 22 consecutive neonates were observed prospectively as a control group; they received a standard nursery formula containing 400 units/liter of vitamin D_3 and no other supplement of vitamin D or its metabolites. Actual vitamin D_3 intake varied during the first five days of life from 0 to 100 units/day. Eight subsequent premature neonates received a standard nursery formula containing 400 units/liter of vitamin D_3 but also were treated orally with 2 μg/kg/day of $25OHD_3$, beginning within the first 12 hours of life and continuing daily for a total of five days. Vitamin D_3 intake varied from 0 to 85 units/day during the first five days of life. The $25OHD_3$ was supplied as a liquid dissolved in medium-chain triglycerides.

In this study, normocalcemia was defined as a serum level of Ca^{++} consistently greater than or equal to 3.0 mg/dl; hypocalcemia was defined as a level of Ca^{++} less than 3.0 mg/dl that was associated with a Ca_T level less than 7.0 mg/dl. A serum level of Ca^{++} less than 3.0 mg/dl was chosen as the definition of hypocalcemia because of previous observation that most neonates with a serum Ca^{++} level less than 2.5 mg/dl have observable symptoms and some premature neonates with serum Ca^{++} levels between 2.5 and 3.0 mg/dl have observable symptoms, whereas patients with Ca^{++} levels greater than 3.0 mg/dl have not been observed to be symptomatic.

All neonates who became hypocalcemic were treated with supplemental intravenous or oral calcium salts. Formulas were supplemented to a 4:1 ratio of calcium to P for infants who were asymptomatic and able to consume greater than 75 ml/kg/day of formula. Intravenous supplement of 500 mg/kg/day of calcium gluconate was given by constant infusion to symptomatic infants and those unable to take adequate volumes orally. Supplementation was stopped when the infant had normal serum Ca^{++} and Ca_T levels for two consecutive days and was taking formula at a rate greater than 75 ml/kg/day. This occurred in all infants who had had supplementation by the end of the first week of life.

Serial morning urine samples were obtained for estimation of urinary calcium and creatinine concentrations. Serial serum levels of glucose, bilirubin, SGPT, and serum urea nitrogen (SUN), as well as CBC counts, were obtained to monitor for untoward effects of the $25OHD_3$ treatment.

Sera for 25OHD determination were collected throughout the study period from 30 normal, maternal–term-infant pairs on day 1 of life as a comparison with the levels of 25OHD in the premature neonates studied.

Analytical methods for serum and urine as well as normal values have been described previously.[6,22,23] Serum levels of 25OHD represent the total level in serum of 25-hydroxyergocalciferol ($25OHD_2$) plus $25OHD_3$. This was measured by a competitive protein-binding radioassay after preparative chromatography. Intra-assay variability is 5% or less, and inter-assay variability is 7% or less.

Statistical analysis (using the Student t test) and correlation coefficients were determined on a computer.

RESULTS

Of the 22 premature neonates in the control group, 11 became hypocalcemic (50%), with serum Ca^{++} concentrations less than 3.0 mg/dl and Ca_T values less than 7.0 mg/dl on day 2 of life. Of the eight premature infants treated with $25OHD_3$, one became hypocalcemic (12.5%). For the purposes of analysis, the control group was separated into a control-normocalcemic group (N = 11) and a control-hypocalcemic (N = 11) group. Maternal and neonatal characteristics and month of birth for each of the three groups (control-normocalcemic, control-hypocalcemic, and $25OHD_3$-treated) are given in Table 1. Data are expressed as mean ± 1 SD. There are no differences among the three groups of premature neonates in maternal age or maternal serum level of Ca_T, Mg, P, or 25OHD on the day of delivery. The month of birth reveals no seasonal importance. Neonatal weight, gestational age, and Apgar scores after five minutes are not statistically different, although the control-hypocalcemic group tended to have lower Apgar scores after five minutes than did the other two groups.

Laboratory data for the three groups of neonates are presented in Table 2. In all premature neonates studied, neonatal day 1 serum level of 25OHD correlated with maternal serum level of 25OHD ($r = .53$, $P < .01$). There was no correlation found between maternal or neonatal day 1 25OHD level and neonatal day 1 Ca^{++} or Ca_T levels.

In the control group, day 2 Ca^{++} and

Ca_T levels differ, by definition, between the normocalcemic and hypocalcemic neonates ($P < .01$). The Ca^{++} and Ca_T values on day 3 and day 5 do not differ between the control-normocalcemic and control-hypocalcemic groups because the hypocalcemic infants were being treated with supplemental calcium during this period. Day 14 Ca^{++} and Ca_T values do not differ between the control groups, although the control-hypocalcemic premature neonates had not been receiving calcium supplements for at least seven days.

Serum 25OHD levels did not differ between the normocalcemic and hypocalcemic control groups on days 1, 5, and 14. Serum 25OHD levels in the entire control group increased slightly ($P < .05$) between the first and 14th day of life, with the standard nursery formula as the only source of vitamin D_3.

The $25OHD_3$-treated group did not differ from the control groups with respect to neonatal day 1 Ca^{++}, Ca_T, P, and 25OHD levels.

In the $25OHD_3$-treated group, one of the eight prematures became hypocalcemic (12.5%), with a day 2 Ca^{++} level of 2.52 mg/dl and Ca_T level of 5.75 mg/dl. This infant received supplemental calcium along with the $25OHD_3$ from day 2 to day 5 of life. The Ca^{++} and Ca_T data from day 3 and day 5 on this infant are excluded from the $25OHD_3$-treated column in Table 2.

Serum Ca^{++} and Ca_T levels increased during the first three days of life in the $25OHD_3$-treated group, reaching levels higher than those seen in control-normocalcemic infants by day 3 ($P < .001$) and day 5 ($P < .05$). Serum levels of 25OHD at least doubled after one oral dose of 25OHD (2 μg/kg) in all three of the neonates in whom an assay was performed on days 1 and 2. Serum values of 25OHD in the $25OHD_3$-treated group rose from day 1 levels (mean ± 1 SD) of 14.5 ± 7.2 ng/ml to day 5 levels of 39.8 ± 18.4 ng/ml and these levels were maintained after treatment was discontinued on day 5, to reach a level of 32.2 ± 11.2 ng/ml on day 14. Serum 25OHD levels on day 5 and day 14 are significantly higher ($P < .001$) in the

Table 1.—Characteristics of the Premature Neonates*

	Control Groups		
	Normocalcemic (N = 11)	Hypocalcemic (N = 11)	$25OHD_3$-Treated Group (N = 8)
Maternal Data†			
Age, yr	21.9 ± 4.6	23.8 ± 4.4	22.3 ± 5.0
Serum Ca_T, mg/dl	9.30 ± 0.9	9.20 ± 0.4	9.24 ± 1.11
Serum P, mg/dl	3.3 ± 0.5	3.9 ± 0.7	4.0 ± 0.7
Serum Mg, mEq/liter	1.59 ± 0.19	1.48 ± 0.17	1.38 ± 0.17
Serum 25OHD, ng/ml	14.4 ± 5.4	16.9 ± 6.7	14.9 ± 7.2
Infant's birth, mo			
No. born May-October	5	7	4
No. born November-April	6	4	4
Neonatal data‡			
Weight, g	1,475 ± 186	1,430 ± 273	1,445 ± 281
Gestational age, wk	32.8 ± 1.9	31.4 ± 2.1	33.4 ± 1.9
Apgar score	9, 6-10	9, 1-10	9, 6-10

*Ca_T, indicates total calcium level; P, phosphate; Mg, magnesium; 25OHD, 25-hydroxyvitamin D.
†Mean ±1 SD.
‡Mean ±1 SD except Apgar score (which was determined five minutes after birth); this is given in median and range.

Table 2.—Neonatal Laboratory Data*

	Control Groups		
	Normocalcemic (N = 11)	Hypocalcemic (N = 11)	$25OHD_3$-Treated Group (N = 8)
Day 1			
Serum Ca^{++}, mg/dl	3.59 ± 0.45	3.54 ± 0.49	3.62 ± 0.41
Serum Ca_T, mg/dl	8.15 ± 1.19	7.54 ± 1.06	8.24 ± 1.18
Serum, P, mg/dl	5.9 ± 0.6	6.5 ± 0.9	5.5 ± 1.2
Serum Mg, mEq/liter	1.87 ± 0.34	1.56 ± 0.34	1.55 ± 0.16§
Serum 25OHD, ng/ml	13.1 ± 3.6	14.3 ± 6.4	14.5 ± 7.2
Day 2			
Serum Ca^{++}, mg/dl	3.46 ± 0.22	2.90 ± 0.20‖	3.55 ± 0.47
Serum Ca_T, mg/dl	8.07 ± 0.93	6.44 ± 0.36‖	8.22 ± 1.23
Serum Mg, mEq/liter	1.46 ± 0.12	1.58 ± 0.38	1.82 ± 0.29
Day 3			
Serum Ca^{++}, mg/dl	3.56 ± 0.31	3.79 ± 0.38	4.08 ± 0.23¶
Serum Ca_T, mg/dl	8.28 ± 0.35	7.98 ± 1.11	9.02 ± 0.67
Serum Mg, mEq/liter	1.70 ± 0.24	1.79 ± 0.19	1.97 ± 0.27
Day 5			
Serum Ca^{++}, mg/dl	3.57 ± 0.37	3.77 ± 0.41	3.92 ± 0.28§
Serum Ca_T, mg/dl	8.83 ± 0.96	9.25 ± 0.73	9.55 ± 0.98§
Serum Mg, mEq/liter	1.84 ± 0.26	2.08 ± 0.17	1.95 ± 0.33
Serum 25OHD, ng/ml	12.2 ± 3.2	15.6 ± 6.6	39.8 ± 18.4¶
Day 14			
Serum Ca^{++}, mg/dl	4.17 ± 0.39	4.19 ± 0.27	4.54 ± 0.31
Serum Ca_T, mg/dl	9.42 ± 0.78	9.48 ± 0.88	9.72 ± 0.79
Serum Mg, mEq/liter	1.92 ± 0.31	1.89 ± 0.26	1.66 ± 0.14§
Serum 25OHD, ng/ml	15.2 ± 5.7	18.1 ± 6.8	32.2 ± 11.2

*Ca^{++}, indicates ionized calcium; Ca_T, total calcium; P, phosphate; Mg, magnesium; 25OHD, 25-hydroxyvitamin D. All values given are mean ±1 SD.
†Hypocalcemic patients received intravenous or oral calcium supplementation between day 2 and day 5 of life.
‡Day 3 and day 5 calcium data do not include values from one patient who became hypocalcemic and received supplementation.
§$P < .05$ different from control normocalcemic mean value.
‖$P < .01$ different from control normocalcemic mean value.
¶$P < .001$ different from control normocalcemic mean value.

$25OHD_3$-treated group than in either of the control groups. Mean day 14 Ca^{++} and Ca_T values are higher in the $25OHD_3$-treated group than in the control groups, but not significantly higher.

Day 5 values for 25OHD in the $25OHD_3$-treated group ranged from 20.8 to 75.5 ng/ml, with the lowest value being found in the one infant in the group who became hypocalcemic.

Serum levels of glucose and bilirubin and need for oxygen and phototherapy were no different among the groups. Approximately half of control and treated premature infants required oxygen supplementation to maintain arterial Po_2 greater than 50 mm Hg, and two thirds of all patients received phototherapy for hyperbilirubinemia. Complete blood cell counts and SGPT and SUN values remained normal in the treated patients. Urinary calcium to creatinine ratios remained less than 0.25 in all treated neonates before, during, and after treatment.

Normal term pregnancies (N = 30) showed maternal and neonatal day 1 sera 25OHD levels of 22.2 ± 7.2 ng/ml and 20.6 ± 3.4 ng/ml, respectively. These values are significantly greater ($P < .001$) than serum 25OHD values in the maternal and premature neonate pairs of the study groups.

COMMENT

Early neonatal hypocalcemia occurs in approximately 35% to 50% of premature neonates, depending on weight, gestational age, and perinatal factors. Many of these neonates remain without observable symptoms, although changes in neurologic function and EEG resulting from hypocalcemia may occur; however, these are quite difficult to evaluate in the premature infant. Neonates who are symptomatic from hypocalcemia may manifest seizures, apnea, neuromuscular irritability, vomiting, abdominal distention, poor feeding, cyanosis, and additional nonspecific symptoms. Treatment of hypocalcemic neonates is accomplished by the intravenous infusion or oral administration of calcium salts. These methods of treatment have caused considerable problems. Infants receiving intravenous calcium are subject to changes in cardiac rate, and severe local damage can occur if calcium salts extravasate into the tissues.[24-26] Oral calcium treatment has been associated with gastrointestinal irritation, increased stool frequency, and lack of success in raising serum calcium level. The prevalence of this disorder, the potential severity of the symptoms, and the morbidity of the treatment available suggest the need for more efficacious treatment methods or prevention of this derangement in calcium homeostasis.

Hypocalcemia in the premature neonate, as in older infants and children, is rarely due to inadequate calcium in the body but rather is the result of an inability to absorb or mobilize calcium from intestinal lumen or bone to the vascular space. This defect in restoration of calcium homeostasis is due to lack, or excess, or decreased effectiveness of one or a combination of the three hormones responsible for calcium metabolism: $1,25(OH)_2D$, PTH, and calcitonin. Each of the hormones has been implicated in one way or another, but a complex interaction of the three calcium-regulating hormones is probably responsible for the ultimate serum calcium level. Whether or not decreased levels of $1,25(OH)_2D$ are part of the origin of this disorder, vitamin D metabolites, more potent than the parent compound, might be expected to be effective, as in other hypocalcemic states, in raising serum calcium level by increasing the gastrointestinal absorption of calcium or by enhancing PTH effectiveness in mobilizing calcium from bone.

Serum levels of 25OHD in mothers and their normal term newborns are substantially greater than levels in mothers and their premature neonates. This may be related to increased metabolism or decreased formation of 25OHD in these mothers of premature neonates. It has previously been reported that maternal serum 25OHD level is lower between 30 to 40 weeks' gestation than earlier in pregnancy.[19] Others have reported no correlation between gestational age and serum 25OHD level.[20,21] A plausible explanation for our findings and those already reported would be a decreasing level of 25OHD during midgestation, reaching a nadir at 36 weeks of pregnancy and increasing to term. Longitudinal, prospective studies will be necessary to establish this. Another possible explanation is the relationship of low serum level of 25OHD to other factors of nutrition and socioeconomic status, which correlate with the incidence of premature deliveries. Low serum 25OHD level may be associated with other metabolic disturbances that ultimately result in premature birth.

In this study, there was no difference in maternal or neonatal serum 25OHD level between the control-normocalcemic and control-hypocalcemic groups. Although there is no correlation between serum 25OHD level and subsequent development of hypocalcemia, we have not evaluated a sufficient number of untreated premature neonates with 25OHD levels of greater than 20 ng/ml to judge whether a low level of 25OHD places the premature neonate at greater risk of experiencing early neonatal hypocalcemia.

There is no correlation in this study, as in others, between serum 25OHD level and Ca^{++} or Ca_T values on the first day of life. This is not a surprising finding, in that fetal Ca^{++} level is primarily determined by an active placental pump of calcium from maternal to fetal circulation and is probably not directly under the control of maternal or fetal calcium-regulating hormones.

The use of oral $25OHD_3$ in the dosage of 2 μg/kg/day was associated with an increase in Ca^{++} and Ca_T concentration during the first three days of life in seven of eight neonates treated. Oral $25OHD_3$ was well tolerated and absorbed. Serum 25OHD levels increased after one dose of $25OHD_3$ (2 μg/kg) in all of the three premature neonates whose 25OHD levels were assayed on days 1 and 2 and in all treated neonates from day 1 to day 5 of life. The range of day 5 levels of 25OHD from 20.8 to 75.5 ng/ml suggests individual variation in rate of absorption or metabolism of the $25OHD_3$ administered. The one neonate in the treated group who

became hypocalcemic had the lowest day 5 serum 25OHD level and the smallest increase in serum 25OHD level from day 1 to day 5 of life.

The $25OHD_3$-treated group had significantly higher levels of Ca^{++} and Ca_T than did the control groups on day 3 and day 5 of life. There was no hypercalcemia or hypercalciuria associated with this rise in serum calcium. Furthermore, there were no other untoward effects of the $25OHD_3$-treatment detected during the first two weeks of life.

The use of oral $25OHD_3$ as the choice of vitamin D preparation in the premature infant may be optimal because it bypasses the possibility of decreased 25-hydroxylase activity in the neonatal liver, while allowing the 1-α-hydroxylase of the kidney to modulate formation of the more potent hormonal form of the vitamin, $1,25(OH)_2D_3$. Large doses of vitamin D itself have been used successfully in term newborns to prevent a decrease in serum calcium level during the first week of life.[27] This treatment method would likely be less effective in premature infants than use of one of the more recently available metabolites of vitamin D. However, this early work in the use of vitamin D in newborns predated the recent discoveries in vitamin D metabolism and should be noted as the first hormonal approach to the prevention of neonatal hypocalcemia.

Because of the effectiveness of $1,25(OH)_2D_3$ in managing other disorders in which there is hypocalcemia,[28,29] its use has been advocated to treat and prevent neonatal hypocalcemia.[8,30] The efficacy and potential risks of this more potent hormone will need to be determined and compared with those of $25OHD_3$ in the future.

The exact mode of action of the $25OHD_3$ is not known, but most probably it functions physiologically to increase formation of $1,25(OH)_2D_3$ and thus increases gastrointestinal absorption and bone mobilization of calcium. A direct pharmacologic effect of $25OHD_3$ is possible but would most probably require higher dosage and serum levels to create a noteworthy increase in serum calcium level. Determination of serum levels of $1,25(OH)_2D$, when available, will help to define more fully the mode of action of this drug and the physiology of this disorder.

We report preliminary data of effective prevention of early neonatal hypocalcemia with oral $25OHD_3$ in premature neonates. Future studies must expand the number of patients treated and add neonates of varying gestational ages, weights, and severity of perinatal asphyxia and neonatal disease. Also, optimal dosage level and minimal duration of treatment must be determined. Further study of vitamin D metabolism in the perinatal period will add to the understanding of the pathophysiology and possible prevention of early neonatal hypocalcemia in the premature.

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Fetal Hydantoin Syndrome in Triplets

A Unique Experiment of Nature

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• **Birth defects associated with phenytoin and phenobarbital taken during pregnancy include craniofacial and limb deformities. These anomalies were found in various degrees of severity in triplets born to a mother taking phenobarbital and phenytoin for an epileptic disorder, giving us a unique opportunity to recognize different manifestations of the hydantoin syndrome in infants that presumably were exposed to the same level of the drugs. These infants were trizygotic and their clinical manifestations varied widely, suggesting the possibility that genetic background may play a significant role in the susceptibility of the fetus to phenytoin and phenobarbital during pregnancy.**

(*Am J Dis Child* 132:978-979, 1978)

During the past decade, there has been growing concern over the teratogenic effects of phenytoin. Extensive and detailed accounts of the birth defects associated with these drugs have been published,[1-3] leaving little doubt about the association of phenytoin with specific abnormalities, particularly craniofacial and limb deformities.[4,5] The role of anticonvulsants in the etiology of congential anomalies is still a controversial issue. We think that through a unique experiment of nature in a multiple pregnancy, some light may be shed on understanding the participation of anticonvulsants and perhaps other factors such as genetic predisposition in the manifestations of the hydantoin syndrome.

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REPORT OF CASES

A 25-year-old gravida 1 para 0 woman had been treated for three years, including the time of her pregnancy, with phenobarbital, 150 mg three times a day, and phenytoin, 100 mg three times a day, for a focal motor seizure disorder. She was also receiving 325 mg of thyroid hormone daily, and chlorpromazine (Thorazine), 50 mg, at night. She was known to be mildly mentally retarded and had a heart murmur. One brother had died in infancy of congenital heart disease, and epilepsy was present in previous generations of the maternal grandmother's family.

The mother was transferred to Wesley Medical Center for delivery because of triplet gestation and premature rupture of membranes with onset of labor. The infants were delivered by cesarean section.

Examination of the placentas and membranes disclosed double chorions and amnions for each common membrane. For the purpose of identification, the infants were assigned letters A, B, and C according to the order of birth. Triplets A and B shared one placental mass; triplet C had a separate placenta. The infants were premature, 32 weeks' gestation, developed respiratory distress syndrome, and recovered after three to four days of oxygen therapy.

Triplet A.—Birth weight of this girl was 1,490 g; length, 42 cm. Apgar scores were 7 at one minute, 7 at five minutes, and 7 at ten minutes. Distinguishing features included a low bridge of the nose, ocular hypertelorism, elevated and bifid xyphoid, and nail hypoplasia of the upper and lower limbs. Roentgenograms of the hands and feet were unremarkable. Serum phenytoin and phenobarbital levels one day after birth were 8 and 12 μg/ml, respectively. Follow-up for 22 months has shown developmental delay. Follow-up data on all three triplets are summarized in Table 1.

Triplet B.—Birth weight of this boy was 1,760 g; length, 43 cm. Apgar scores were 6 at one minute, 7 at five minutes, and 9 at ten minutes. Clinical findings included ocular hypertelorism, undescended testes, digitalization of the right thumb, and partial fusion of the saggital suture. Roentgenograms of the hands and feet

Table 1.—Growth and Development at Age 22 Months*

	Triplet		
	A	B	C
Length, cm	78.9	79	76.4
Percentile	< 5th (7th)	< 5th (< 5th)	< 5th (< 5th)
Weight, g	10,230	9,920	8,850
percentile	13th (20th)	< 5th (5th)	< 5th (< 5th)
Personal-social,† mo	15	12	11-12
Language,† mo	15	12	10
Gross motor,† mo	15	13	14

*Corrected age of 20 months shown in parentheses.

†Denver Developmental Screening Test data.[11]

Table 2.—Birth Defects Associated With Phenytoin

	Triplet A	B	C
Growth and development retardation	+	+	+
Craniofacial abnormalities			
Large fontanels	−	−	+
Craniosynostosis	−	+	−
Ocular hypertelorism	+	+	+
Depressed nasal bridge	+	+	+
Cleft lip and palate	−	−	+
Limb abnormalities			
Nail hypoplasia	+	+	+
Distal phalangeal hypoplasia	−	+	+
Finger-like thumb	−	+	+
Other skeletal abnormalities			
Prominent bifid xyphoid	+	−	−

showed poorly ossified distal phalanges. Serum phenytoin and phenobarbital levels at 1 day of age were 5 and 8 μg/ml, respectively. Follow-up for 22 months has shown significant developmental delay and deformity of the skull associated with craniosynostosis.

Triplet C.—Birth weight of this girl was 1,500 g. Apgar scores were 3 at one minute, 5 at five minutes, and 8 at ten minutes. The child was limp and cyanotic at birth. This infant was the most severely affected of the three, with marked ocular hypertelorism, low bridge of the nose, bilateral cleft lip and palate, a large anterior fontanel, and nail hypoplasia. Serum was qualitatively positive for phenytoin and phenobarbital. Follow-up for 22 months showed significant developmental delay. The cleft lip and palate have been surgically repaired. All three infants have been referred to a stimulation program.

COMMENT

Numerous reports over the past nine years have shown that the craniofacial and limb deformities present in these triplets represent some of the abnormalities found in the hydantoin syndrome: synostosis, low bridge of the nose, cleft palate, nail hypoplasia, and digit abnormalities.[6]

Of the anticonvulsant drugs associated with definite teratogenesis, phenobarbital and phenytoin have been named as the most prominent,[7] but it would appear that phenytoin is probably the chief culprit in the formation of congenital anomalies. There is a pattern of congenital anomalies that appear to be characteristic. The abnormalities of these triplets were very similar to those that have been reported, particularly the craniofacial and limb abnormalities listed in Table 2.[1,2,8]

These three children represent a rather unique experiment of nature since all three children as fetuses were likely to have been exposed to the same levels of phenobarbital and phenytoin. It is evident that these triplets were actually trizygotic, as one of the girls had red hair while the other girl had darker hair. The second baby was a boy, so undoubtedly these children are all products of different ova, leaving open the question of participation of genetic predisposition to the teratogenicity of phenytoin and phenobarbital.[9]

Considering the different manifestations of the hydantoin syndrome of these triplets, one might think that possibly there was a difference of intrauterine blood flow distribution and therefore of drug exposure; however, the birth weights were within 270 g of each other, and this would suggest that there was no significant difference in blood flow.

Of interest is the genetic background of these triplets, including most significantly a family history of congenital anomalies as well as epilepsy. In order to examine this background, an extensive investigation of the family tree was done. It disclosed a number of abnormalities, including epilepsy in several generations, congenital heart disease, "stubby fingers," mental retardation, and cleft lip and palate, which may be relevant to the cases presented here. It has been suggested that epileptic seizures per se could be the cause of congential anomalies; however, without drugs, convulsions do not seem to cause malformations.[9]

Undescended testes, as in the case of triplet B, is part of such a varied number of congential dysmorphic syndromes that it is difficult to assign it to the hydantoin syndrome; Pinto et al[10] reported two cases of abnormal genitalia as part of the fetal hydantoin syndrome. The nail hypoplasia and digital abnormalities of these triplets were characteristic and very similar to those depicted in pictures previously published.[1,2,5]

We believe these triplets represent a unique experiment of nature, showing that the exposure to phenytoin will not necessarily result in the same congenital anomalies, or teratogenesis. In this case, although all three fetuses were exposed to the same serum level of phenytoin and phenobarbital, the differences in manifestations of hydantoin syndrome would suggest there is some form of genetic predisposition for this to happen. When counseling prospective mothers about the possibility of congenital defects associated with the taking of anticonvulsant drugs, the history of congenital anomalies similar to those reported in the hydantoin syndrome should be considered.

Timothy Gatschet helped obtain photographs of the triplets. Gertrude Suenram helped prepare the manuscript.

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Do We Support Parents of High-Risk Infants?

A Survey

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• **The establishment of regional neonatal intensive care units has reduced physical and mental handicaps in premature infants, but has caused emotional and psychological strain on parents because of frequently lengthy separation of mother and child. The study was undertaken to learn what is currently being done to support parents of high-risk infants.**

A questionnaire survey showed that prenatal screening was performed by only a few institutions. Not all nurseries employed full-time social workers. Such full-time status was no guarantee that all parents were interviewed and given support. Furthermore, requests for public health nurses to make predischarge and postdischarge home visits were not universally made.

(*Am J Dis Child* 132:980-983, 1978)

In recent years, modern methods and new techniques used during the perinatal period have significantly improved the chance of survival for the high-risk infant. The incidence of serious physical and mental handicaps among these infants has been also reduced. These improvements are due in part to the establishment of regional neonatal intensive care units. Many infants admitted to these units have been transported for many miles from the place of delivery and are consequently separated from their mothers for extended periods of time. This early and lengthy separation may interfere with or adversely affect the formation of a satisfactory relationship between the mother and her infant, or disrupt the family.[1-3] This premise may be supported by the fact that parental abuse of low-birth-weight infants is much higher when compared to full-term infants.[4,5]

In many intensive care units, measures are taken to reduce the impact of the separation of the parents from their infant and to help them to overcome the emotional stress surrounding the birth of a high-risk infant. This is attempted by providing parental support during the weeks and months afterwards.

This study was undertaken to learn what is currently being done in the neonatal centers to support parents of high-risk infants and to identify parents at risk for child abuse.

METHODS

A questionnaire to be completed by physicians in neonatal intensive care units was constructed from the literature on parent-child interactions. Questions were designed to elicit two types of information: first, the early identification of parents with potential for child abuse, and second, what was being done to support the parents of prematurely born infants. Thirty-three questions requiring short or yes/no answers were used. Questionnaires with covering letters explaining the purpose of the study were sent to the 360 pediatricians listed in the American Academy of Pediatrics section on Perinatal Pediatrics.

RESULTS

A total of 175 completed questionnaires were returned. This represents 48.6% of the physicians to whom a questionnaire was mailed.

More than half (56.1%) of the responding pediatricians reported that they were full-time faculty in either a university hospital or in a university-affiliated hospital. An additional 15% were based full time in hospitals but had no university appointment.

The times when screening for potential child abuse was performed either in a formal or informal manner are depicted in Fig 1.

More than half (55.5%) of the respondents said that a full-time social worker was available in the nursery. The activities of these full-time social workers with regard to

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parent contact are illustrated in Fig 2.

The 19.8% of full-time social workers who made no home visits talked to all the parents and, in addition, requested that home visits be made by the public health nurse. The pattern of public health nurse visits is depicted in Fig 3.

Parent helpers were used by 30% of the pediatricians who answered the questionnaire. In the nurseries where parent helpers were used, nearly half (47.8%) conducted parent support meetings.

Almost all (94.2%) respondents stated that the hospital had 24-hour visiting privileges. All respondents encouraged parents to touch and handle the infant as soon after birth as possible, while almost all allowed parents to actively participate in caring for the infant.

If the parents did not visit their baby, they were contacted by all nurseries. The time lapse before contact varied, but ranged from one day to seven days. The most frequent time for parent contact was between two and three days.

Seventy percent responded positively to the question: "Do you have any educational meetings for parents on how to care for and handle the child and what to expect and when?" Eighty-seven percent reported that they hand out printed material to parents.

Clergy were actively involved in parent support activities in 78.1% of the nurseries.

Sixteen percent responded to the question about child abuse of neonates who had been discharged from their own neonatal center. The estimates were that up to 5% of these children had been abused. All but one respondent to the child abuse questions used prenatal screening; all used nursery screening techniques and employed a full-time social worker. In these nurseries, the social worker repeatedly talked to parents, made predischarge and postdischarge home visits, and used the public health nurse.

COMMENT

This questionnaire was sent to the pediatricians listed in the section on Perinatal Pediatrics of the American Academy of Pediatrics. It is presumed that these pediatricians have positions of leadership and the majority undoubtedly are actively involved in patient care in neonatal intensive care units.

In 1976, Michigan recorded approximately 3,650 cases of suspected physical abuse and approximately 21,500 cases of suspected child neglect, which means that in that year approximately 1% of Michigan's children were suspected to have been abused or neglected (H. Hofstra, oral communication, September 1977). This corresponds well with US statistics.[6]

Baldwin and Oliver[7] in their 1975 United Kingdom study found that 21% of the abused children had been prematurely born. Fomufod[4] quotes several studies in which the proportion of abused children who were premature or low-birth-weight infants ranged from 27.8% to 44%. A review of cases seen at the Montreal Children's Hospital showed that 23.5% had been of low birth weight, in contrast to 7% to 8% low-birth-weight rate in Canada during the same year.[5] The present survey shows an up to 5% estimated incidence of child abuse in prematures.

Much has been written about child abuse. Only recently have articles and books appeared that deal with prevention.[8] Prenatal screening for potential abusing parents is not as yet universally done.

Kempe[9] developed an observation list for the physician's office or prenatal clinic. He states that if prenatal observations are not possible, then much of this information can be obtained on the first postpartum day.

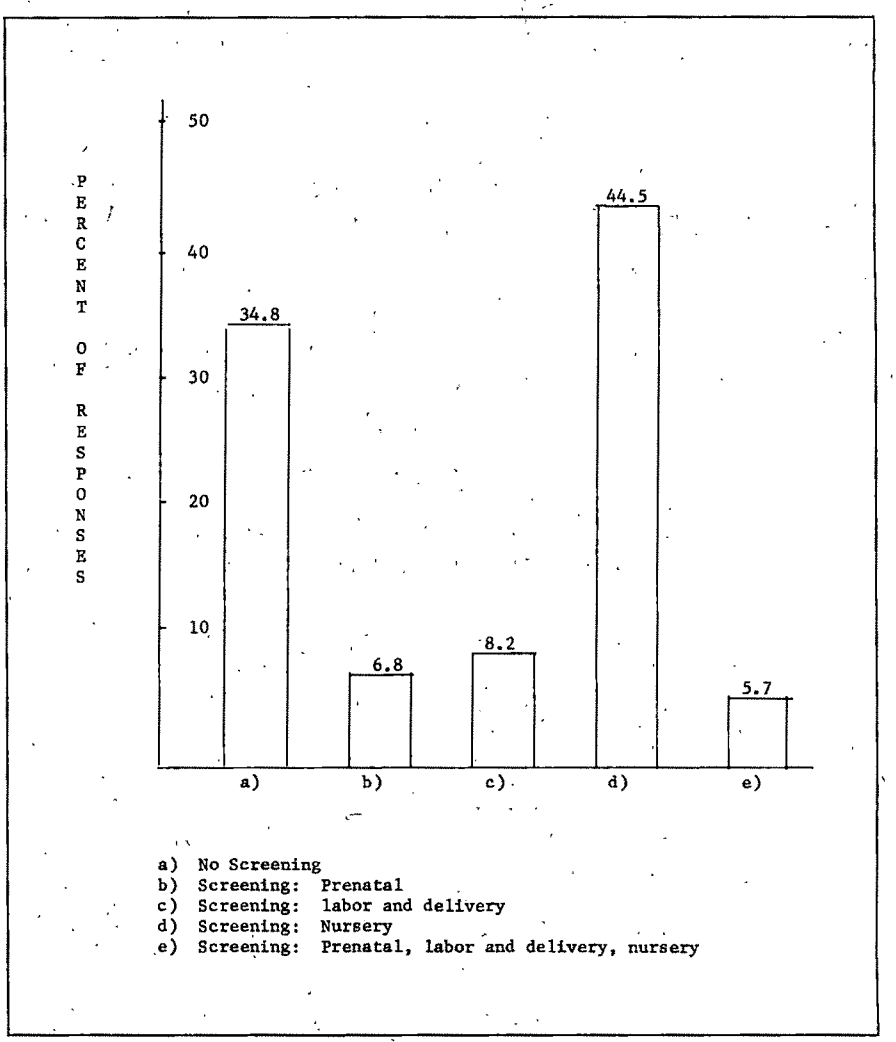


Fig 1.—Time of screening for potential child-abusing parents.

ROYAL COLLEGE OF

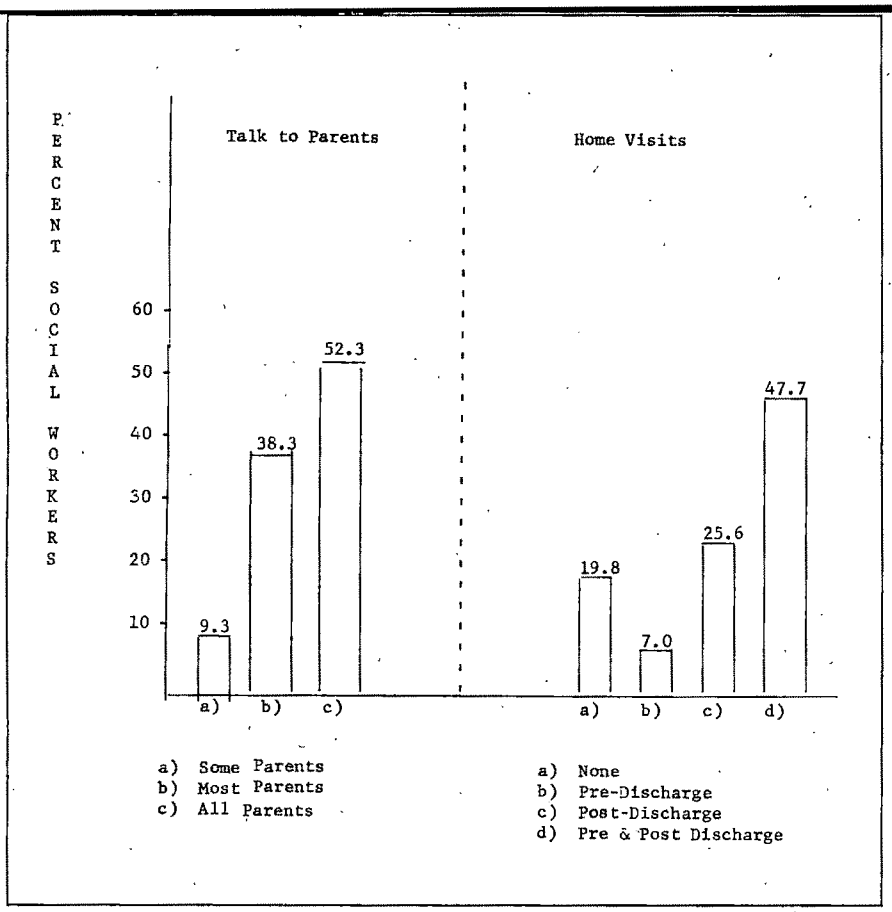


Fig 2.—Parent contact by full-time social workers.

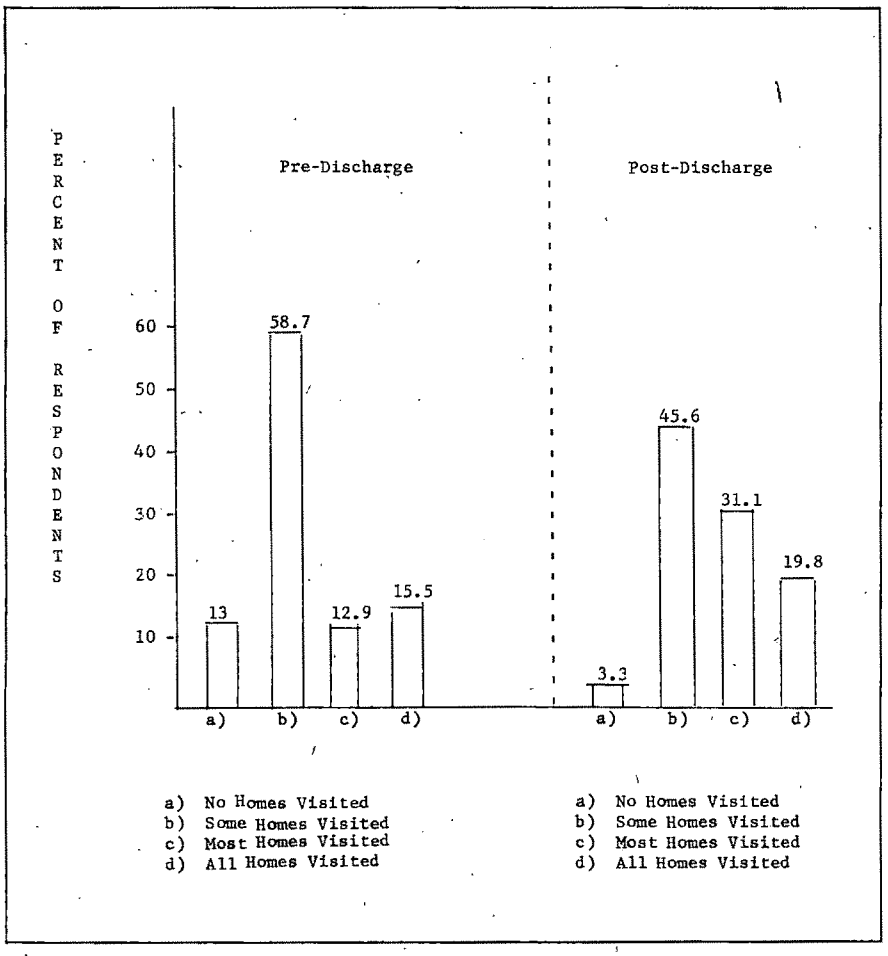


Fig 3.—Requests for home visit by public health nurse.

He reports, "We ask our nurses to look at the mother (and the father, if he is present) and answer just three questions: How does she look, what does she do, what does she say."

Screening can be performed by many people. The social worker can be very helpful. Our survey showed that not all nurseries employed full-time social workers and full-time status was no guarantee that all parents were interviewed and provided support. Many, however, made predischarge and postdischarge home visits, indicating that the evaluation of the home is given certain priority.

Figure 3 shows the requests for public health nurses to visit the homes. It appears that she generally has not been accepted as an important member of the "neonatal team." The survey did not disclose whether the home visit was actually made by the public health nurse. She can and should play a major role especially where infants are transferred over great distances since she is the most available of all professional community health workers. Wilson[10] called the public health nurse a "neglected resource." Besharov[11] believes prevention of child abuse is a community process and responsibility. Parents need to be told where they can seek help when they need it, eg, family service agencies, self-help groups, or visiting nurses.

Cropley and Bloom[12] developed a "parent-staff interaction guide" that helps staff and rotating house officers make a smooth transition from shift to shift. It provides a record of telephone inquiries, visits, involvement of the parents, etc. Fifty-two percent of our respondents used a "guestbook," which parents sign every time they visit their infant. The signing of this book gives them the impression that they are guests, very welcome, and that their presence is appreciated. It is an accurate check on parents' visiting habits and may help to identify parents who may neglect their chil-

dren. When visits are impossible on account of distance, telephone contacts should be recorded in such a book.

Our survey showed that 24-hour visiting privileges are now an accepted phenomenon and that parents are encouraged to touch their infants. Both practices encourage and strengthen parent-infant bonding and hopefully will reduce child abuse.

Parent helpers were used by a small percentage of the respondents. Many parents are relieved at the opportunity to talk about their feelings so that they can be helped to deal with them.[13] Stone[14] remarks, "Sharing the consequent anxiety with an informed and sympathetic listener (both qualities are required) cannot remove maternal concern—nor should it—but ineffectual brooding and self-blame can be helped in the direction of more rational acceptance and effective planning." Kempe[15] states in a thought-provoking article that psychiatrists do no better than our "mothering aides and family aides who have had training in two different ways: they have had a loving father and mother, and they have been a loving father or mother. They have not gone to any courses, they have not had any indoctrination."

SUGGESTIONS

Hospitals could make available a room where weekly parent meetings can be held. These meetings are not only educational, but are primarily intended to bring together parents who have infants in the nursery (a member of the staff should be present), allowing parents to ask questions and raise anxieties in the company of other parents with like experiences; this helps to reduce feelings of isolation that many parents have. Parents whose children are on the way to recovery can be quite supportive of others more acutely stressed.

The nursing, medical staff, and others must receive instruction and in-service education in understanding and effective intervention in the process of grief and mourning. They should develop skills in observing parents, interviewing, listening, advising, and reassuring. In short, they should be familiar with most aspects of crisis intervention.

The costs of these programs are not prohibitive. Some activities, such as those of parent helpers, can be performed by volunteers. Mileage costs for home visits could be reimbursed. Special project grants may be a source for these funds, so that the only real cost would be in the personal energy required to organize the program. However, for these organizers the personal rewards should far outweigh the efforts spent.

Ray Helfer, MD, Michigan State University, and Winnie Willis, RN, MPH, University of Michigan, School of Public Health, reviewed the manuscript and gave advice.

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Prenatal Diagnosis of Congenital Nephrosis in 23 High-Risk Families

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• **The efficacy of maternal serum and amniotic fluid alpha-fetoprotein (AFP) estimation for the prenatal detection of congenital nephrosis was assessed in 23 pregnancies of couples with a previously affected child. At 15 to 18 weeks' gestation, amniotic fluid AFP concentration was elevated in seven of 23 cases, and maternal serum AFP level in five of these. Legal abortion was carried out at 18 to 19 weeks in all those cases where the amniotic fluid AFP concentration was abnormally high, and in all cases the fetus was found to be affected. The diagnosis of intrauterine congenital nephrosis was obvious by electron microscopic examination of the fetal kidney, but not by light microscopy. The child was born without congenital nephrosis in all 16 cases where amniotic fluid AFP level was normal, and in 16 of 18 cases (89%) where maternal serum AFP concentration was normal. Thus, the amniotic fluid AFP assay is more reliable and is recommended whenever congenital nephrosis is suspected on the basis of family history.**

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Congenital nephrosis (CN) is inherited as an autosomally recessive trait.[1] Children with CN may live severely handicapped as long as two to three years, but no specific treatment can be offered. Recent studies indicate that CN is manifested during early fetal life, and recently the disease has become accessible to prenatal diagnosis on the basis of elevated amniotic fluid alpha-fetoprotein (AFP) levels.[2-8] Congenital nephrosis has been described in most parts of the world, and the gene frequency is particularly high in Finland where the estimated incidence of CN in newborns is 12.4/100,000.[9]

In our previous study,[5] we brought up the question of appropriate diagnosis of CN in aborted fetuses, since it was not obvious by light microscopic examination of the fetal kidney. In this article we extend this consideration to include fetuses aborted with intra-amniotic prostaglandin, and report our results on the efficacy of prenatal diagnosis of CN based on both maternal serum and amniotic fluid AFP measurements.

MATERIALS AND METHODS

Twenty-three couples with an earlier child with CN sought genetic counseling and prenatal diagnosis in their subsequent pregnancy. In each case, the diagnosis of the index child was based on clinical and morphological findings, including high placental-fetal weight ratio, proteinuria, and oedema as well as characteristic histological and ultrastructural changes of the kidney specimens obtained at autopsy.[10]

In the subsequent pregnancy, maternal serum sample was taken for the AFP assay prior to amniocentesis at 15 to 18 postmenstrual weeks, and amniocentesis was performed after ultrasonographic localization of the placenta and the fetus. Twenty milliliters of amniotic fluid was drawn, and the AFP concentration and fetal karyotype were determined in all samples. No chromosome abnormalities were detected. The AFP concentrations in maternal serum and amniotic fluid were estimated by radioimmunoassay as previously described.[11] Normal values for maternal serum and amniotic fluid AFP levels were derived from studies of a large number of pregnancies with a normal fetal outcome.[12] Alpha-fetoprotein values above the normal 97.5 percentile were considered abnormal. Pregnancies with normal AFP levels were advised to continue. Delivery records of these cases were sent to us and the newborns were examined by the pediatrician of the delivery hospital and later followed up at the well-baby clinics.

RESULTS

Sixteen cases had normal AFP values both in amniotic fluid and maternal serum (Fig 1 and 2), and all these women were delivered of a healthy baby at term. No postnatal evidence

for CN was found. Seven cases showed elevated AFP levels in amniotic fluid (Fig 1). Repeated amniocentesis was done in three cases and the abnormal AFP result was confirmed. Maternal serum AFP level was above the 97.5 percentile in five cases. Two patients had a normal serum AFP level, but the amniotic AFP levels were elevated.

The seven pregnancies with elevated amniotic fluid AFP levels were terminated. Termination was carried out by hysterotomy in five cases and with intra-amniotic prostaglandin F2α in two cases. Autopsy was performed on all fetuses. No gross external or internal anomalies were found. The kidneys were macroscopically normal. Histological examination of the kidneys showed a normal overall picture with normally progressing nephronogenesis in the subcapsular portion of the cortex and more mature glomeruli deep in the cortex. It was very difficult to find pathological changes by light microscopy. Slight mesangial cell hyperplasia seen in the maturing glomeruli, an abundance of resorption droplets in the proximal tubuli, and occasional dilated cortical tubuli were suggestive features. Electron microscopic investigation of the deeply located, most mature glomeruli allowed the conclusive diagnosis of CN to be made. A characteristic feature was the loss of foot processes of visceral epithelial cells (Fig 3). Occasionally, blunted foot processes had remained in many capillary walls, but the overall picture was clearly different from age matched controls (20 fetuses in the range of 16 to 20 weeks' gestation) showing distinct foot processes (Fig 4).

An additional characteristic electron microscopic feature was the accumulation of basement membrane-like material in the mesangial areas. The diagnosis was more complex in those cases where termination was carried out by prostaglandin induction. In both cases, the kidneys were autolysed thus hampering the electron microscopic examination. In one case, it was impossible to ascertain the diagnosis based on the absence of foot processes, but the accumulation of mesangial basement membrane-like material on electron microscopy was suggestive of CN. In the other case, it was possible to demonstrate the foot process fusion despite partial autolysis (Fig 5).

COMMENT

Our findings on pregnancies at risk of fetal CN clearly demonstrate that the amniotic fluid AFP assay is a reliable test for detecting fetal CN at the 16th to 18th week of gestation. The number of affected fetuses was seven of 23, which is roughly compatible with the expected 1:4 ratio. The cases reported in the literature[2-8] bring the number of prenatally detected CN fetuses to 13 and so far

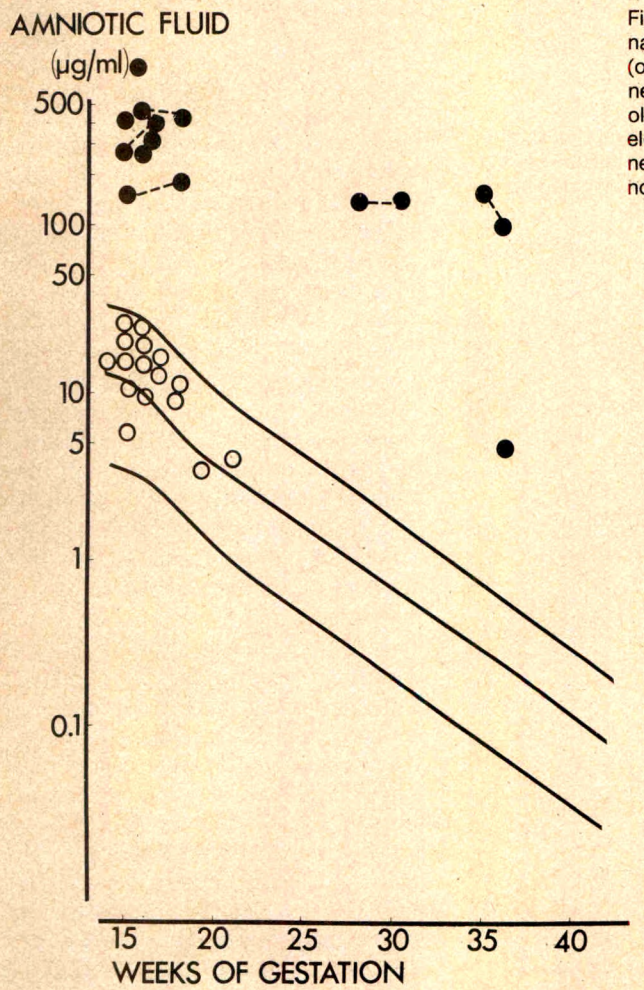


Fig 1.—Amniotic fluid alpha-fetoprotein concentrations in pregnancies at risk of having another child with congenital nephrosis (open circle indicates healthy child and solid circle, congenital nephrosis of fetus after termination of pregnancy). Three cases older than 25 weeks' gestation were coincidentally found to have elevated AFP levels and children were born with congenital nephrosis. Solid lines represent 97.5, 50, and 2.5 percentiles of normal distribution.

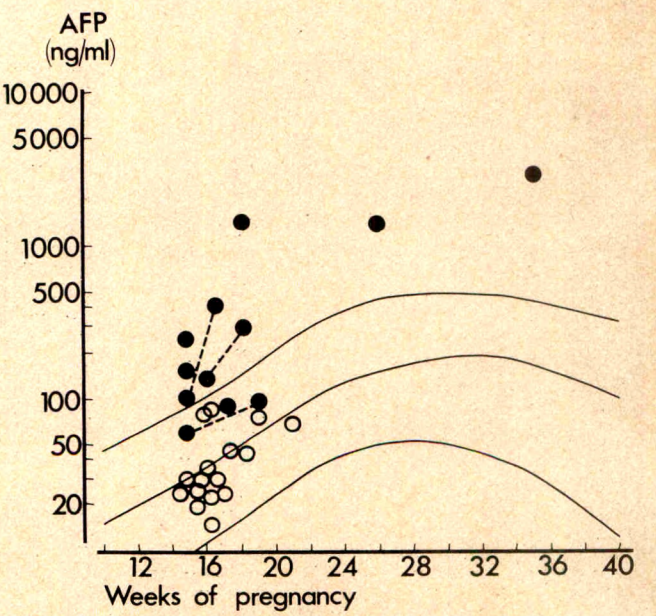


Fig 2.—Maternal serum AFP concentrations in pregnancies at risk of having another child with congenital nephrosis (open circles indicate healthy child and solid circles, congenital nephrosis of fetus after termination of pregnancy). Solid lines represent 97.5, 50, and 2.5 percentiles of normal distribution.

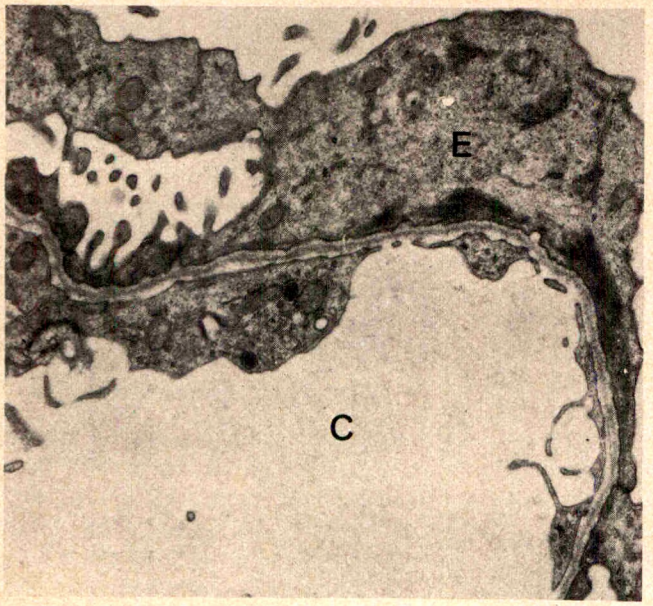


Fig 3.—Peripheral capillary of glomerulus from fetus with congenital nephrosis. Basement membrane is thin and covered by continuous epithelial cytoplasm (C indicates capillary lumen and E, cytoplasm of epithelial cell, lead citrate and uranyl acetate staining, original magnification ×20,000).

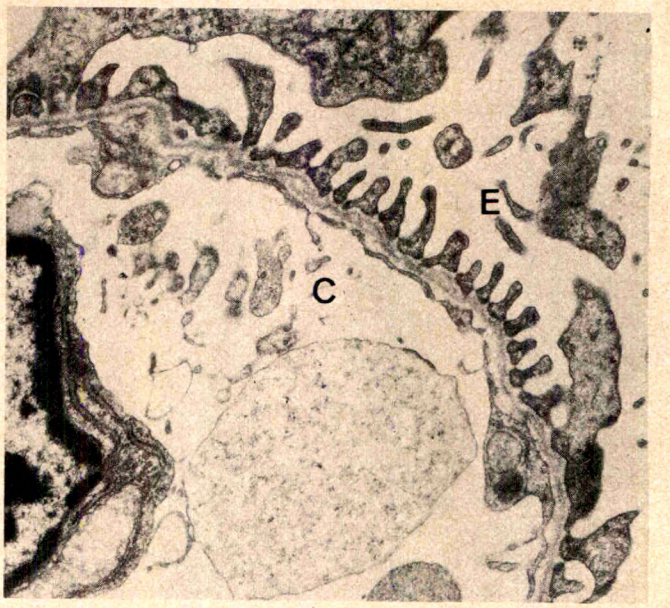
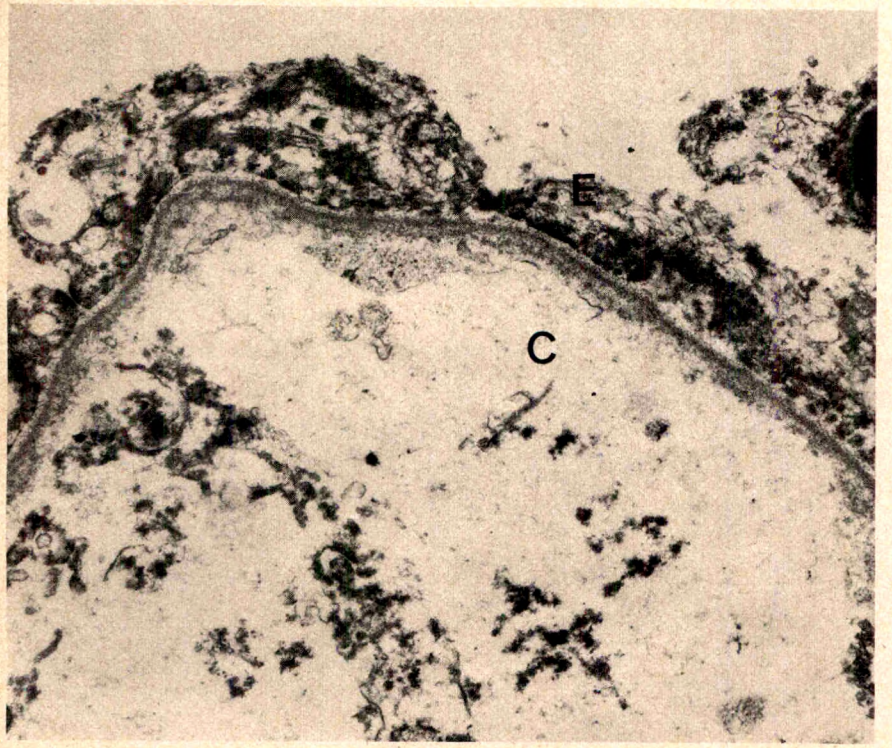


Fig 4.—Electron microscopic picture of normal fetal kidney. Note distinct foot processes covering epithelial aspect of basement membrane (C indicates lumen and E, epithelial side of glomerular wall, lead citrate and uranyl acetate staining, original magnification ×20,000).

Fig 5.—Capillary wall of glomerulus from fetus aborted by prostaglandin induction. Details are partly destroyed by autolysis, but foot process retraction can still be seen (C indicates capillary lumen and E, epithelial cell cytoplasm covering basement membrane, lead citrate and uranyl acetate staining, original magnification ×20,000).



there have been no false-negative results by amniotic fluid analysis. False-positive results were not found either. In screening studies for neural tube defects, false-positive results have been encountered in a wide variety of conditions.

As in the case of neural tube defects, incorrect estimation of the gestational age is the most obvious source of error, and this should carefully be evaluated before any decision to interrupt the pregnancy is taken. It is also important to confirm the results of prenatal studies in the newborn or in the aborted fetus. In this respect, CN poses special problems as the demonstration of characteristic changes in the fetal kidney requires electron microscopy and experience with this rare disease. In the absence of a neural tube defect or any other overt malformation, the possibility of CN must be considered as a cause of elevated AFP level. In three additional cases, elevated amniotic fluid AFP levels in the third trimester were related to neonatal CN (Fig 2). This substantiates the association

between elevated AFP levels and postnatal CN. Although rare, CN exists in most parts of the world and it has also been described in a population with a high incidence of neural tube defects.[7]

The loss of foot processes is a nonspecific change found in clinical and experimental conditions associated with heavy proteinuria and nephrotic syndrome. In the fetus, it provides evidence for a kidney disease and proteinuria and, thus, is a sufficient criterion for the presence of CN.

When abortion has been induced with prostaglandins, autolysis of the fetal tissues may mask specific changes. This was clearly demonstrated in two of our cases also. It is likely that saline induction of abortion would cause autolysis of fetal tissues and obscure the diagnosis of CN.

Our data and those reported in the literature suggest that the majority of CN cases would be detected by maternal serum AFP screening. This occurred in five of seven cases (71%) between 15 and 18 weeks' gestation. Maternal serum AFP level in CN shows a steep and rapid increase between the 16th and 18th week, and some cases with an initially normal AFP level may show an abnormal value at the 18th week as demonstrated by one case in our material. For detecting CN in the fetus maternal serum, AFP screening should preferably be carried out close to the 18th gestational week.

Even in high incidence areas of Finland, the incidence of CN is much lower than the incidence of neural tube defects in the United Kingdom. Therefore, experience obtained in the British Collaborative Study[13] for screening of neural tube defects by maternal serum AFP assay warrants critical consideration before screening for fetal CN is undertaken. However, studies from the United Kingdom[14,15] and Sweden[16] indicate that, aside from neural tube defects and CN, there are other types of fetal pathologic findings and obstetric complications that might be detected by maternal serum AFP screening in the second trimester. Whereas the question of a feasible screening program awaits trials on susceptible populations, our results show that the AFP assays in maternal serum and amniotic fluid will certainly be of great benefit to high-risk families who have borne a child with CN.

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Prolonged Nitroprusside and Intermittent Hemodialysis as Therapy for Intractable Hypertension

Alfredo J. Elberg, MD; Helen M. Gorman, MB, BCh; Rex Baker, MS; A. José Wenger, MD; José Strauss, MD

• **Nitroprusside was used with intermittent hemodialysis over a 26-day period in a 6-year-old boy with intractable hypertension. Hemodialysis effectively removed thiocyanate from the blood, thus preventing its accumulation and subsequent toxic manifestations. Prolonged nitroprusside infusion maintained arterial blood pressure at acceptable levels until the patient became responsive to other antihypertensive therapy.**

(Am J Dis Child **132:988-989, 1978)**

Sodium nitroprusside has become recognized as an effective drug for the emergency management of severe hypertension in both adults[1-4] and children.[5,6] One of its end products, thiocyanate (SCN), has been shown to have hypotensive properties in high doses.[7] However, the therapeutic hypotensive effect of nitroprusside is a result of its free nitroprusside radical rather than of its metabolic end products.[1,2] Toxic effects of SCN include fatigue, nausea, severe vomiting, psychotic behavior, muscle spasms, hepatic necrosis, skin rashes, tinnitus, and hypothyroidism.[1-4,8-10] One or more of these may force early discontinuation of nitroprusside therapy. Fatalities have occurred at SCN plasma levels of 20 mg/dl.[8] This report shows that removal of SCN by intermittent hemodialysis may allow administration of nitroprusside over a prolonged period of time.

REPORT OF A CASE

A 6-year-old boy with nephrotic syndrome secondary to membranous glomerulopathy was admitted to Jackson Memorial Hospital, Miami on Nov 12, 1975, for management of severe hypertension; his arterial blood pressure was 200/150 to 130 mm Hg. He weighed 21 kg and his creatinine clearance was 52 ml/min/1.73 sq m. After admission, treatment with furosemide plus different combinations of methyldopa, propranolol hydrochloride, guanethidine sulfate, and diazoxide was relatively ineffective. On the fifth day after admission, addition of nitroprusside infusion at rates of 1.0 to 5.5 μg/kg/min lowered blood pressure in less than one minute after beginning the infusion. Arterial blood pressure was maintained within normal limits until the 11th day when nitroprusside therapy had to be discontinued because of vomiting and hallucinations associated with elevated plasma SCN levels (11.5 mg/dl). Thiocyanate level was determined by the colorimetric method described by Pettigrew and Fell.[11]

While the patient was receiving multiple drug therapy, creatinine clearance had decreased to 38 ml/min/1.73 sq m, and plasma renin activity was 30 ng/ml/hr (supine), with 24-hour sodium excretion of 45 mEq. Twenty-five days after admission, continuous infusion of nitroprusside was reinstituted; nine days later, plasma SCN level was 9.6 mg/dl (Table) and inexorable fluid retention (resistant to furosemide) led to congestive heart failure, pulmonary edema, and cardiac arrest. Hemodialysis was performed to remove the excess fluid. Cardiac status improved and plasma SCN level decreased to 3.8 mg/dl. Nitroprusside therapy was then continued without interruption for 17 additional days without toxic manifestations. Blood pressure range was 140/110 to 110/80 mm Hg. During that time dialysis was repeated four times to

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Effect of Hemodialysis on Blood Thiocyanate Levels

Days After Admission	Blood Thiocyanate Levels, mg/dl			Hemodialysis	
	Predialysis	Middialysis	Postdialysis	Flow, ml/min	Duration, hr
34	9.6	...	3.0	200	5.0
35	3.5	...	1.0	200	5.0
41	5.5	...	1.0	170	4.5
46	14.8	6.3	2.0	170	4.0
49	7.4	3.1	1.7	200	4.0

remove SCN. Renal function improved (creatinine clearance, 90 ml/min/1.73 sq m) and the child responded to furosemide. Oral minoxidil, guanethidine, and furosemide controlled blood pressure satisfactorily, and he was discharged in stable condition. This was maintained at home with the addition of propranolol two weeks after discharge. Six months later the patient was leading an active life; diastolic blood pressure ranged between 80 and 100 mm Hg.

COMMENT

Nitroprusside was discovered in 1850,[12] in 1929 it was reported to have hypotensive properties, and it has been used for the management of hypertension at least since 1951.[1] It has a high therapeutic index, it acts rapidly, and its action disappears shortly after discontinuation of the drug; tachyphylaxis has rarely been noted.

The mechanism of action of nitroprusside seems to be through relaxation of vascular smooth muscle, principally that of the "resistance" arterial vessels.[3-7] It is metabolized to cyanogen, which is rapidly converted to SCN in the liver by the enzyme rhodanese.[2] In adults with normal renal function, the half-life of SCN is seven days; it is eliminated only through the kidney.[2] SCN is transformed into cyanide by the erythrocytic enzyme thiocyanate oxidase.[13]

Although some of the toxic effects of nitroprusside may be due to cyanide,[9] most are caused by SCN accumulation.[3] Therefore, careful monitoring of plasma SCN levels in patients receiving nitroprusside over long periods is mandatory. In general, when plasma SCN reaches a potentially toxic level (5 to 10 mg/dl),[3] or when the patient exhibits toxic manifestations nitroprusside therapy should be discontinued. An alternative to discontinuation of nitroprusside therapy is rapid removal of SCN to avoid its accumulation in blood. This can be achieved by hemodialysis[8,14] because SCN is distributed mainly in the extracellular compartment[14,15]; only one third is protein bound, and it has a low molecular weight.[15]

This case, to our knowledge, is the first report of a child with renal failure who received such high doses of nitroprusside over such a prolonged period of time without toxic manifestations. When this patient first received nitroprusside therapy, it had to be discontinued after six days because of toxic manifestations related to high SCN levels (11.5 mg/dl). In contrast, when it was used the second time, the addition of intermittent hemodialysis permitted continuous nitroprusside infusion for 26 days. Therapy was then discontinued, not because of complications, but because the patient did not need it.

Elevated blood pressure refractory to all other antihypertensive agents and aggravated by intractable fluid retention was reduced to tolerable levels (diastolic pressure, 90 to 100 mm Hg). It was maintained without any evidence of SCN having toxic effects until the patient became responsive to diuretics and other antihypertensive drugs. In this manner, bilateral nephrectomy[16] or death may have been avoided.

In conclusion, the combination of prolonged nitroprusside therapy and intermittent hemodialysis seems to be a good approach to the management of severe refractory hypertension in pediatric patients, especially when renal function is decreased.

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Roger F. Palmer, MD, professor and chairman, Department of Pharmacology, University of Miami, helped in the determination of thiocyanate level and the reviewing of the text; the nursing and house staff of the Pediatric Intensive Care Unit, Jackson Memorial Hospital, Miami, helped care for the patient; and Vincent Finlay gave technical assistance.

Nonproprietary Names and Trademarks of Drugs

Diazoxide—*Hyperstat.*
Methyldopa—*Aldomet.*
Sodium nitroprusside—*Nipride.*

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Recurrent Acute Suppurative Thyroiditis

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• Two patients had two recurrent episodes each of acute suppurative thyroiditis. Circulating concentrations of plasma thyrotrophin, thyroxine, and triiodothyronine were within the range of normal. Antibodies to thyroid microsome or thyroglobulin were not found. Anaerobic bacteria such as *Bacteroides, Peptostreptococcus,* and *Peptococcus* were identified as causative agents, indicating that anaerobic organisms may play an important role in the pathologic process. The present cases are the third and fourth reported cases of recurrent acute suppurative thyroiditis in the literature.

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Acute suppurative thyroiditis is very rare, particularly in children. Only two cases of recurrent acute suppurative thyroiditis, to our knowledge, have been documented in the literature.[1-3] Thus, we wish to describe in detail two patients with two recurrent episodes of acute suppurative thyroiditis; of special interest has been the infecting organism.

REPORT OF CASES

CASE 1.—An 8-year-old boy was admitted to hospital because of a painful swelling in the anterior part of the neck. One week prior to admission, fever, cough, and sore throat were noted. In a few days, swelling in the anterior part of the neck developed with accentuation of the neck pain. Results of the examination showed a swelling in the area of the left lobe of the thyroid gland. The mass was 5 × 5 cm, firm, and tender. The overlying skin was erythematous. The remaining results of the physical examination were unremarkable.

The hemoglobin level was 13.5 g/dl. The WBC count was 6,800/cu mm, with 44% neutrophils. The ESR was 60 mm in the first hour. The serum cholesterol level was 210 mg/dl. Plasma thyrotrophin (TSH), triiodothyronine (T_3), and protein-bound iodine (PBI) values were 3.1 μU/ml, 108 ng/dl and 8.1 μg/dl, respectively. The resin T_3 uptake (RT_3U) was 29.3%. The thyroid uptake with iodine 131 (^{131}I) was 8.5% after 24 hours. The thyroid scan showed no activity over the left upper lobe of the thyroid gland. The tender, swollen area was aspirated with a needle, and *Bacteroides* and *Peptostreptococcus* grew from culture of the purulent material.

The patient received 500 mg of oral cephalexin and 500 mg of oxacillin sodium daily. The mass decreased in size and the signs of inflammation subsided. He became well and was discharged.

At the second admission, four years after discharge, he was readmitted with a four-day history of fever, sore throat, and neck pain. On physical examination, a tender, firm mass was palpable in the area of the left lobe of the thyroid gland. The overlying skin was erythematous. The remaining results of the physical examination were normal.

The hemoglobin level was 12.1 g/dl. The WBC count was 10,300 per cu mm, with 66% neutrophils. The ESR was 64 mm in the first hour. The serum cholesterol level was 145 mg/dl. Plasma TSH, thyroxine (T_4), T_3, and PBI values were 1.2 μU/ml, 11.4 μg/dl, 170 ng/dl, and 6.6 μg/dl, respectively. The RT_3U value was 28.7%. Antibodies never developed against thyroid microsome or thyroglobulin. The thyroid scan showed no activity over the left lobe of the thyroid gland (Fig 1).

Treatment was begun with 250 mg of oral cephalexin every six hours. Since the patient remained febrile for the next three days, the cephalexin was replaced by intravenous oxacillin sodium at the same dose. Despite the chemotherapy, the mass became enlarged and fluctuant. It was incised and a large amount of the foul, purulent material was drained. *Peptostreptococcus* grew from culture of the pus. Within 24 hours after surgery, the patient's temperature returned to a normal level. The hospital course was uneventful; he became well and was discharged.

CASE 2.—An 8-year-old boy was admitted for evaluation of induration in the anterior part of the neck. About one month before admission, he had fever, cough, and sore throat. A week later, he noticed a painful, tender swelling in the anterior part of the neck. The mass became enlarged and more painful, and he was admitted to another local hospital, where he received antibiotics. Subsequently, the size of the mass decreased and the fever subsided. On admission, results of a physical examination showed a firm, nonfluctuant, 4 × 4-cm

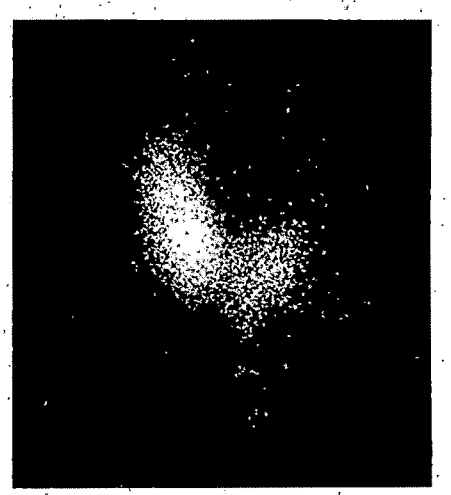


Fig 1.—Scintigram of thyroid using sodium pertechnetate Tc 99m at second episode in case 1.

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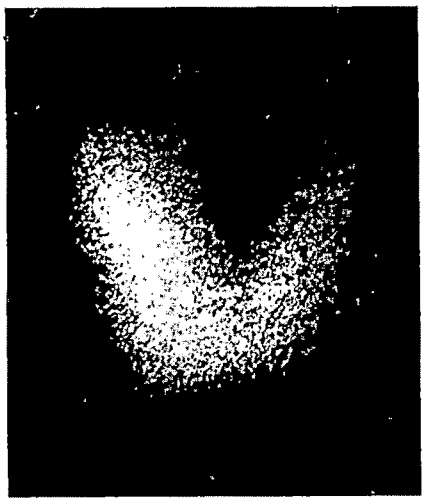


Fig 2.—Scintigram of thyroid using sodium pertechnetate Tc 99m at second episode in case 2.

mass in the area of the left lobe of the thyroid gland. The overlying skin was slightly erythematous. The remaining results of the physical examination were unremarkable except for noticeable dental caries.

The hemoglobin level was 12.7 g/dl. The WBC count was 6,300/cu mm, with 26% neutrophils. The ESR was 22 mm in the first hour. The serum cholesterol level was 225 mg/dl. The plasma TSH and T_4 levels were 5.7 μU/ml and 7.4 μg/dl, respectively. The RT_3U value was 37.7%. The thyroid uptake value with ^{131}I was 37% for 24 hours. The thyroid scan showed decreased activity over the left lobe of the thyroid gland. The mass was aspirated with a needle and bacteria failed to grow from a culture of the material.

The patient received 100 mg of oral minocycline hydrochloride daily for ten days and he responded well. He was discharged on the 15th hospital day in good condition.

At the second admission, three months after discharge, he was readmitted to the hospital because of a painful swelling in the anterior part of the neck and pain on swallowing or extending the neck. Three days before readmission, fever and sore throat were noted. The results of a physical examination showed that a firm, 5 × 3-cm, tender mass was palpable in the area of the left lobe of the thyroid gland. The remaining results of the physical examination were unremarkable except for noticeable dental caries.

The hemoglobin level was 12.8 g/dl. The WBC count was 11,500/cu mm, with 61% neutrophils. The ESR was 78 mm in the first hour. The serum cholesterol level was 117 mg/dl. The plasma levels of TSH, T_4, and T_3 were 7.2 μU/ml, 7.8 μg/ml, and 108 ng/dl, respectively. The RT_3U was 38.3%. Antibodies to thyroid microsome or thyroglobulin were not found. The thyroid scan showed sharply diminished activity in the left lobe of the thyroid gland (Fig 2).

Treatment was begun with 900 mg of oral erythromycin daily. Despite the chemotherapy, the mass became gradually erythematous and fluctuant. Incision and drainage were performed on the sixth hospital day. *Peptococcus* that was sensitive to erythromycin grew from culture of the purulent material. Postoperatively, the patient again received 900 mg of oral erythromycin daily and his condition improved rapidly.

COMMENT

Acute suppurative thyroiditis is far less common than other clinical types of thyroiditis such as subacute thyroiditis and Hashimoto's thyroiditis. Kirkland et al[4] reported in 1973 that only five cases of this disease in children have been documented in the literature in the English language since 1950.

The present cases show two interesting clinical features of this disease: recurrent episodes and infecting organisms. Only two cases of recurrent acute suppurative thyroiditis were available in the literature.[1-3] Thus, the present cases add further examples of recurrent acute suppurative thyroiditis. The rarity of acute suppurative thyroiditis may be due to the remarkable degree of local resistance of the thyroid gland to bacterial infection. Live streptococci and staphylococci injected directly into the thyroid gland of dogs are reported to result rarely in suppuration.[5] The relatively high concentration of the iodine within the thyroid gland may provide an unfavorable environment for bacterial growth. One can only speculate as to why our patients had two attacks of this rare disease. The recurrent episode in the same area of the thyroid gland may imply the underlying abnormality in thyroid structure or the presence of a thyroglossal duct. It, however, remains obscure in our cases.

The most interesting aspect of the present cases is the infecting organism. Anaerobic bacteria such as *Bacteroides*, *Peptostreptococcus*, and *Peptococcus* were identified as causative agents of acute suppurative thyroiditis. *Bacteroides* and *Peptostreptococcus* have been rarely reported.[4,6,7] However, *Peptococcus* has not been previously described as a possible pathogen. These findings suggest that anaerobic bacteria may play an important role in the pathogenesis of acute suppurative thyroiditis and they indicate the need for clinical awareness of these anaerobic bacteria as potential causes of this disease. In contrast to the present findings, however, it has been generally accepted that the most common bacteria involved in acute suppurative thyroiditis are *Streptococcus hemolyticus*, *Staphylococcus aureus*, and *Pneumococcus*.[8] Szego and Levy[2] and Olambiwonnu et al[3] reported *Streptococcus viridans* as a pathogen. The frequent use of antibiotics may modify the infecting organism involved in this disease.

Our cases provide some information regarding thyroid functions in this disease. Only a few reports are available using modern techniques in the assessment of circulating thyroid hormone levels.[7-9] In accord with other findings,[7-9] circulating levels of plasma TSH, T_4, and T_3 were within the range of normal, and antibodies against thyroid microsome or thyroglobulin were not detected. These results are in keeping with the absence of clinical signs of hypothyroidism or hyperthyroidism in our patients.

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Treatment of Acute Otitis Media of Infancy With Cefaclor

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• **The emergence of ampicillin-resistant *Haemophilus* as a clinical problem in otitis media necessitates a search for alternative, effective therapy. An orally absorbable cephalosporin derivative, cefaclor, is equally effective in vitro against ampicillin-susceptible and -resistant *Haemophilus* and against other bacteria that cause acute otitis media. Two dosage schedules of cefaclor (40 and 60 mg/kg/day) were evaluated in 95 infants with acute otitis media. Bacterial origin was determined by a culture of tympanocentesis fluid. Success rates using the smaller dosage were inferior to those using the larger dosage. Results of therapy for pneumococcal and *Haemophilus* infection with 60 mg/kg/day were comparable to those previously found with amoxicillin trihydrate or with combinations of trisulfapyrimadines with erythromycin or penicillin V. One patient with an ampicillin-resistant *Haemophilus* infection responded well to cefaclor and did not have a relapse. Cefaclor was well tolerated and caused an acceptably low incidence of minor, adverse effects. Cefaclor deserves further testing as a candidate for preferred status as a single-drug treatment of acute otitis media.**

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Acute otitis media of infancy presents continuing problems to the physician. For several years, ampicillin, amoxicillin trihydrate, or combinations of sulfonamide drugs with penicillin or erythromycin have been considered standard antimicrobial therapy. However, in recent years, β-lactamase-producing *Haemophilus* organisms have showed up in the nontypable strains from patients with otitis, as well as in the type b strains causing systemic infections.[1-3] Thus, a drug with activity against β-lactamase-producing *Haemophilus* would be desirable. In addition, infants younger than 8 weeks of age may have coliform organisms isolated from middle ear aspirate in 15% to 20% of the cases.[4] These coliform bacilli are often resistant to the previously mentioned drugs.

Cephalexin monohydrate and cephradine, the currently available, orally administered cephalosporin derivatives, have poor activity against most strains of *Haemophilus*[5,6] and, in one study, cephalexin was inferior to ampicillin for otitis media due to *Haemophilus*.[7] Cefaclor, a new cephalosporin derivative, was reputed to have much greater activity against *H influenzae* and an expanded spectrum against *Klebsiella* and *Entero-*

Table 1.—In Vitro Susceptibility of Bacteria to Cefaclor

Organisms Tested	No. Tested	Activity*	Cumulative % of Strains Susceptible to Indicated Concentrations of Cefaclor, μg/ml							
			≤ 0.16	0.31	0.63	1.25	2.5	5	10	20
Reference strains										
Haemophilus influenzae b, β-lactamase positive	16	MIC	NT†	56	88	100	...	...	...	...
		MBC	NT	38	44	81	94	100	...	...
H influenzae b, β-lactamase negative	34	MIC	NT	74	94	100	...	...	...	...
		MBC	NT	24	65	97	100	...	...	...
Tympanocentesis strains										
Haemophilus sp	22	MIC	5	23	50	73	95	100	...	...
		MBC	5	9	27	55	82	91	95	100
Pneumococcus	23	MIC	30	61	100	...	...	...	...	...
		MBC	13	57	100	...	...	...	...	...
Staphylococcus aureus	8	MIC	0	0	38	75	88	100	...	...
		MBC	0	0	25	38	63	75	88	100

*MIC indicates minimal inhibitory concentration; MBC, minimal bactericidal concentration.
†NT indicates not tested.

bacter strains.[5,6]

After confirming the in vitro activity of cefaclor against *H influenzae*, we undertook an evaluation of the drug's clinical efficacy in infants with acute otitis media.

METHODS AND MATERIALS

The study was carried out in the Out-Patient Clinic of Children's Medical Center, Dallas, between November 1976 and January 1978. Infants younger than 18 months of age whose conditions were diagnosed as acute otitis media were enrolled in the study if they had no associated disease and no history of adverse reactions to penicillins or cephalosporins. Signed, informed consent was obtained from a parent for tympanocentesis and cefaclor therapy. The patients had not received antibiotics during the preceding week.

Examination and tympanocentesis were performed under visualization of the tympanic membranes through a Ziess binocular operating microscope. The canal was irrigated with a 1:1,000 benzalkonium chloride solution. Aspiration of middle ear fluid was performed by puncturing the inferoposterior quadrant of the tympanum with a 21-gauge needle connected to a trap and suction. The fluid was inoculated onto 5% sheep's blood agar and chocolate agar media, and into Levinthal broth. After 24 and 48 hours' incubation at 36 °C, subcultures were made from Levinthal broth onto sheep's blood agar and chocolate agar. If there was insufficient fluid for direct plating, the aspirating needle was flushed with Levinthal broth for culture. Identification of bacteria was by standard methods.

Disk susceptibility testing was done by the Kirby-Bauer method using chocolate agar for *Haemophilus* species and blood agar for other bacteria. Zones of inhibition around a 30-μg cefaclor disk were measured after 18 hours' incubation. Broth dilution testing was done in Mueller Hinton broth with 1% Supplement C added for testing *Haemophilus* sp. Twofold dilutions of cefaclor from 20 to 0.16 μg/ml were made and the antibiotic broth inoculated with an estimated 10^5 colony-forming units of bacteria. The minimal inhibitory concentration (MIC) was read visually after 18 hours' incubation at 36 °C, and subcultures of clear tubes were made onto blood agar or chocolate agar for an additional 24 hours' incubation to determine the minimal bactericidal concentration (MBC).

Cefaclor was given to 50 infants in a dose of 40 mg/kg/day and to 50 additional infants in a dose of 60 mg/kg/day in four equally divided dosages by mouth. Treatment was continued for ten days. Five children did not return. The 48 children receiving the smaller dose and the 47 children receiving the larger dose who were seen one or more times at follow-up constitute the study groups. One hour after the first dosage of medication, a finger-prick sample of heparinized blood was taken for assay of cefaclor content by the method previously described.[8]

Patients were requested to return for examination after three and ten days of treatment and again one month later. The appearance of the tympanic membranes under pneumatic otoscopy, symptoms, and possible adverse effects of the therapy were recorded. Laboratory tests before and after treatment included complete blood cell count with platelet estimation, routine urinalysis, BUN, and SGOT determinations.

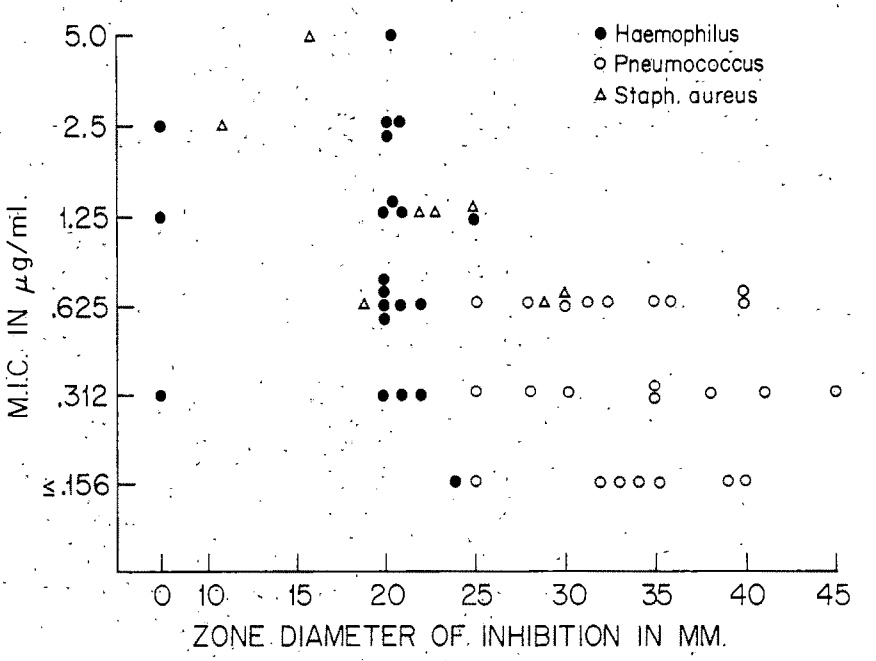
RESULTS

Before the treatment study was initiated, 50 stock strains of *H influenzae* b, originally isolated from patients with meningitis or

Table 2.—Comparative Clinical Features of Study Groups

Characteristic	Cefaclor 40 mg/kg/Day (N = 48)	Cefaclor 60 mg/kg/Day (N = 47)
M	28	22
Race		
Black	25	30
White	12	11
Latin American	10	6
Chinese	1	0
Age, mo		
0-5	17	17
6-11	26	23
12-17	5	7
Bilateral otitis	33	30
Tympanocentesis culture		
Haemophilus sp*	11	8
Pneumococcus	11	10
Haemophilus,* pneumococcus	0	2
Staphylococcus epidermidis	15	12
S aureus	4	4
Others†	2	2
Sterile	5	9

*Indicates 12 nontypable, three type b, four *H parainfluenzae*.
†Indicates three diphtheroids, one *Candida* sp.



Relation between disk (abscissa) and broth dilution (ordinate) susceptibility testing of bacteria from middle ear fluid. MIC indicates minimal inhibitory concentration.

other systemic infections, were tested for in vitro susceptibility to cefaclor (Table 1). All were inhibited by 1.25 μg/ml or less and the 16 β-lactamase-positive strains were as susceptible as the 34 β-lactamase-negative strains.

The treatment groups were comparable regarding age, race, and sex (Table 2). Most patients (66%) had bilateral otitis media. Bilateral otitis was as common in pneumococcal infection (13 of 21 patients or 62%) as in *Haemophilus* infection (13 of 19 patients or 68%). These bacteria, alone or in combination, were isolated from the middle ear fluid of 42 patients (44%). Of these 42 patients, only 14 (15%) had sterile middle ear fluid; eight (8%) had *Staphylococcus aureus*, and 27 (28%) had *S epidermidis* (Table 2).

The pathogens isolated from middle ear fluid were susceptible in vitro to achievable concentrations of cefaclor (Table 1). *Staphylococcus epidermidis* strains were tested only by disk diffusion. Of 32 strains tested, 28 had zones of inhibition of 20 mm or greater (mean, 26.7 mm) and five were not inhibited. The correlation between disk and broth dilution testing results against *Haemophilus*, pneumococci, and *S aureus* is shown in the Figure. Three *Haemophilus* strains with no zone of inhibition around the cefaclor disks were susceptible by broth dilution testing. The mean zone diameter with *Haemophilus* was 13.0 mm, with *S aureus* 21.7 mm, and with pneumococci 33.8 mm.

Only one patient had an infection due to a β-lactamase-producing *H influenzae* that had a MIC and a MBC of 0.63 μg/ml cefaclor. Plasma concentrations of cefaclor one hour after an oral dosage of 10 mg/kg ranged from 1.8 to 14.4 μg/ml (7.0 [mean] ± 0.6 [SEM]) and with the 15 mg/kg dosage they ranged from 1.2 to 23.4 μg/ml (9.0 [mean] ± 0.8 [SEM]).

The clinical results of treatment are summarized in Table 3. Six patients returned for evaluation only on the third day of treatment; their conditions had improved and the otitis was considered to be responding satisfactorily. Cefaclor therapy was discontinued before ten days in eight patients. Three infants had diarrhea and two had a generalized exanthem possibly

Table 3.—Results of Treatment With Cefaclor

Pretreatment Culture	Returned Only for 3-Day Evaluation	Drug Therapy Discontinued Before 10 Days	Evaluation After 10 Days' Therapy: No. of Patients Evaluated	Well	Serous Otitis Media	Drainage	Otitis Media
Haemophilus sp	1	0	18	14	1	1 (Sterile)	2 (1 *Haemophilus*; 1 unknown)
Pneumococcus	1	3 (1 rash; 1 diarrhea; 1 not improved)	17	15	0	1 (*S aureus*)	1 (unknown)
Pneumococcus and *Haemophilus*	0	0	2	2	0	0	0
Staphylococcus epidermidis	2	1 (rash)	24	21	2	1 (not cultured)	0
S aureus	0	2 (diarrhea)	6	6	0	0	0
Other bacteria	1	0	3	2	0	0	1 (pneumococcus)
Sterile	1	2 (1 roseola; 1 gastroenteritis)	11	9	1	0	1 (*S epidermidis*)

Table 4.—Recurrence of Otitis Media After Therapy

Cefaclor Dosage	Patient No.	Pretreatment Culture	Recurrence of Otitis Media: Days After End of Therapy	Culture of Middle Ear Fluid
40 mg/kg/day	1	Pneumococcus	2	Pneumococcus
	2	Pneumococcus	4	Pneumococcus and *H influenzae*
	3	Pneumococcus	14	Pneumococcus
	4	Pneumococcus	20	NC*
	5	Pneumococcus	22	*S epidermidis*, diphtheroids, *S viridans*
	6	*Haemophilus influenzae b*	5	*H influenzae* b and *S epidermidis*
	7	*Staphylococcus aureus*	19	NC
	8	*S epidermidis*	5	NC
	9	*S epidermidis*	9	NC
	10	*S epidermidis*	48	NC
60 mg/kg/day	11	Pneumococcus and *H influenzae*	1	NC
	12	*H influenzae* b	23	Pneumococcus
	13	*H influenzae*	6	NC
	14	*H influenzae*	10	NC
	15	*H parainfluenzae*	3	NC
	16	*S aureus*	20	*Pseudomonas* sp
	17	*S aureus*	21	*H influenzae*
	18	Sterile	12	NC

*NC indicates not cultured.

Table 5.—Comparison of Treatment Regimens

Study and Treatment	Pneumococcal Infection, %			*Haemophilus* Infection, %		
	Cured After 10 Days' Therapy	10-42 Days Otitis Media	Follow-up Serous Otitis	Cured After 10 Days' Therapy	10-42 Days Otitis Media	Follow-up Serous Otitis
1						
Amoxicillin trihydrate	92	32	18	94	8	...
Penicillin V	75	11	6	79	8	15
Erythromycin	82	8	...	65	11	22
Erythromycin and trisulfapyrimadines	74	25	5	93	17	...
2						
Penicillin V	89	30	11	72	27	...
Penicillin V and trisulfapyrimadines	86	25	10	88	40	10
3						
Cefaclor, 40 mg/kg/day	78	71	...	70	17	17
Cefaclor, 60 mg/kg/day	100	...	17	88	50	13

related to the drug. In one infant whose tympanocentesis culture was sterile, a rash consistent with roseola developed, and one child was hospitalized after one day for severe gastroenteritis thought to be unrelated to cefaclor therapy. (Vomiting attributable to cefaclor was not observed.) The condition of a patient with pneumococcal otitis was thought to be unimproved on the third day so cefaclor therapy was discontinued; however, repeated tympanocentesis showed that the pneumococcus was no longer present.

Children were considered cured at the completion of ten days' therapy if the tympanic membrane was translucent, lustrous, and moved well in response to pneumatic otoscopy. If there was persistent fluid in the middle ear without inflammation, they were classified as serous otitis media and, if there was continuing opacity and bulging of the tympanum and redness, they were labeled otitis media and received further antibiotic treatment (usually amoxicillin or erythromycin and trisulfapyrimadines). Five of the 82 patients (6%) evaluated at the tenth day had otitis media and three patients had drainage through a persisting perforation. Of the patients with *Haemophilus* or pneumococcal infection, persisting otitis media or drainage occurred only in those treated with the smaller dose of cefaclor, although one patient treated with 60 mg/kg/day was considered to have serous otitis media. The patient with β-lactamase-positive *Haemophilus* was well at the tenth day and remained well during one month of follow-up.

Recurrence of otitis media during the month after completion of treatment was common (Table 4). Eleven of the 18 relapses occurred in children who had initially had pneumococcal or *Haemophilus* infection. Documented recurrence with the same organism involved in the initial episode was found only in those treated with the 40 mg/kg/day regimen. Recurrences were not treated with cefaclor.

One child whose pretreatment BUN level was 22 mg/dl had a slight increase to 25 mg/dl on the tenth day but this subsequently decreased to 11 mg/dl. Increased leukocyte counts appeared in the urinary sediments of three patients without other evidence of toxic effect on the urinary tract. Eosinophilia of greater than 500/cu mm was found in three patients (942, 980, and 1,023/cu mm).

Mean SGOT values pretreatment were 31.7 IU (±1.7 SEM) and 33.5 IU (±2.7 SEM) posttreatment in children given 40 mg/kg/day of cefaclor. The mean pretreatment and posttreatment SGOT values in infants treated with 60 mg/kg/day were 24.0 IU (±1.0 SEM) and 27.4 IU (±1.4), respectively. Overall, the SGOT value was greater than 40 IU in ten infants before treatment and in 14 infants after treatment. The greatest SGOT value was 108 IU.

COMMENT

In general, the immediate responses to cefaclor of infants with acute otitis media were satisfactory and the drug was well tolerated with an acceptably low incidence of minor, adverse effects. In Table 5, the results in children with pneumococcal and *Haemophilus* infections are compared with responses in two previous studies performed in our clinic. Although these were carried out at different time periods, the protocols and the patient populations were similar so the comparisons should be valid. An exception is that, in the second and third studies, responses were evaluated by one of us (C.M.G.) so there is probably more consistency in the observations than in the first study in which several physicians participated. The first study has been reported[9] but the second study has not. It involved 265 infants and children, including 73 with pneumococcal and 53 with *Haemophilus* infection.

Responses to the 40 mg/kg/day regimen were inferior to those seen in patients who received 60 mg/kg/day of cefaclor. In *Haemophilus* infections, the results with the larger dosage of cefaclor were comparable to those previously found with amoxicillin or with trisulfapyrimadines combined with erythromycin or penicillin V and they were superior to those with the latter two drugs alone or the lower dosage of cefaclor. The lower incidence of recurrent otitis during follow-up in those initially treated with 40 mg/kg/day cefaclor is probably due to the fact that several of those children received amoxicillin at the tenth day of cefaclor therapy because of persisting otitis.

McLinn[10] compared cefaclor with

amoxicillin and found an 83% success rate with amoxicillin and a 91% success rate with cefaclor. He also assayed the antibiotic content of middle ear fluid aspirated during therapy and reported mean concentrations of 0.5 μg/ml cefaclor in 25 patients, 0.3 μg/ml amoxicillin in 47 patients, and 0.4 μg/ml ampicillin in 54 patients. The dosages used are not stated.

Although immediate responses to the course of therapy were good, recurrences within a month of completion of therapy were very common with any regimen. No infant had infection due to coliform bacilli thus, the effect of cefaclor on coliform infection in early infancy could not be evaluated. Only one child had an infection due to an ampicillin-resistant, β-lactamase-producing strain of *Haemophilus*. The patient responded well to cefaclor and did not have recurrence during the follow-up period. Because cefaclor is equally effective in vitro against β-lactamase-positive and -negative strains, it has an advantage over amoxicillin or ampicillin. Some ampicillin-resistant *Haemophilus* would respond to combinations of sulfa drugs with penicillin or erythromycin but this is not uniformly so according to Shurin et al.[1]

If the favorable experience with cefaclor in this study and in the report of McLinn[10] is confirmed by further studies, cefaclor should be a valuable antibiotic for otitis media of infancy with distinct advantages over other available drugs. Because the 40 mg/kg/day regimen had fewer successes and because all documented relapses due to the same bacterial species present before therapy occurred with that dosage, it is recommended that further studies be done with no less than 60 mg/kg/day.

Serum assays for cefaclor were performed by Marion L. Thomas. Thomas R. Tetzlaff, MD and Vanthaya Namasonthi, MD assisted with evaluation of patients.

Nonproprietary Names and Trademarks of Drugs

Amoxicillin trihydrate—*Amoxil, Larotid.*
Cephalexin monohydrate—*Keflex.*
Cephradine—*Anspor, Velosef.*

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CORRECTION

No. of Patients Mistakenly Treated as References.—In the article titled "Delayed Development of Pneumocystis Pneumonia Following Administration of Short-Term High-Dose Trimethoprim-Sulfamethoxazole," published in the May JOURNAL (132:525-526, 1978), in column two, two lines from the bottom and in column three, the first six lines (p 525), the number of patients being treated was mistakenly referred to as reference numbers. The two sentences involved should read as indicated below:

Infectious complications in patients not receiving TMP-SMZ were non-PCP pneumonitis in two and meningitis and/or sepsis in three. Infectious complications seen in patients who received TMP-SMZ were non-PCP pneumonitis in three, oral moniliasis in two, otitis media in two, and suspected but not proved sepsis in one.

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There have been reports of dyskinetic movements of the lips, face, and extremities occurring with the use of Cylert. Convulsive seizures have also been reported. A definite causal relationship between Cylert and these reactions has not been established.

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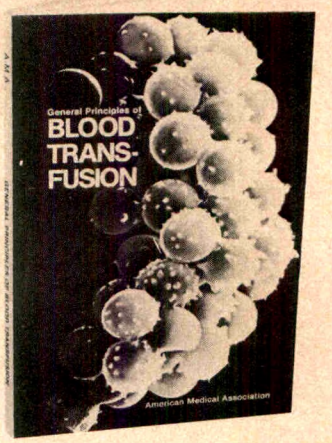
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Serum Bile Acid Levels in Protracted Diarrhea of Infancy

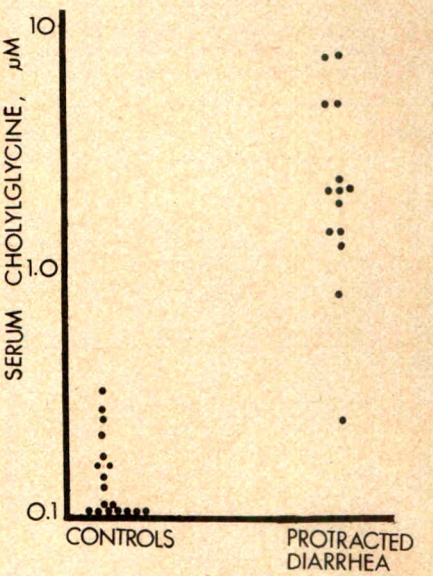
Laurence M. Demers, PhD, John D. Lloyd-Still, MD

• **Significant elevations in two glycine-conjugated serum bile acid levels (cholic and chenodeoxycholic) were detected in a majority of infants with intractable diarrhea of infancy. In contrast, children with chronic inflammatory bowel disease had values of serum bile acids within the normal range. Although intravenous alimentation and constant-infusion elemental diet may alter hepatic function, serum bile acid levels were also elevated in other infants with intractable diarrhea not treated by these methods. We hypothesize that endotoxemia or other unknown mechanisms together with therapy are exerting a detrimental effect on hepatic function.**

(*Am J Dis Child* 132:1001-1003, 1978)

The cause of the protracted or intractable diarrhea syndrome of infancy is usually ill defined. This disorder is characterized by chronic nutritional failure, septic complications, and a high mortality.[1] Bile acid disturbances in the intractable diarrhea syndrome of infancy include an increase in unconjugated bile acids in the duodenum in association with bacterial overgrowth,[2] increased fecal bile acid loss comparable to that following ileal resection,[3] and a reduction in bile salt pool size.[4]

Transitory abnormalities in liver function have been reported in the intractable diarrhea syndrome of infancy and have usually been ascribed to the effects of therapy with intravenous alimentation.[1,5] Liver biopsy specimens show cholestasis.[5-7] Measurement of serum bile acid concentrations has been shown to be one of the most sensitive indices of disturbed hepatic function, especially in the anicteric patient.[8] We are reporting the serum bile acid profile of 14 infants with intractable diarrhea syndrome of infancy.



Serum cholylglycine levels (micromoles per liter) in 14 infants with intractable diarrhea compared to controls.

PATIENTS AND METHODS

Methods

Radioimmunoassay of the glycine-conjugated bile acids—cholylglycine, chenodeoxycholylglycine, deoxycholylglycine, and sulfolithocholylglycine—were performed as previously described by Demers and Hepner.[9] Standards of purified bile acids and patient's sera in dilutions ranging from threefold to 20-fold, depending on serum bile acid concentrations, were reacted with specific antibody against the glycine-conjugated bile acids. Antibodies generated were highly specific for each glycine-conjugated bile acid, with only minimal cross-reactivity (less than 5%) betweeen the individual bile acid forms. The cholylglycine antiserum showed only 18% relative cross-reactivity with cholyltaurine, the chenodeoxycholylglycine antiserum showed 8% cross-reaction with its taurine counterpart, the deoxycholylglycine antiserum cross-reacted with deoxycholyltaurine at 3%, and the sulfolithocholylglycine antiserum showed a 1% cross-reactivity with the taurine derivative. Specific cross-reactivity figures for all bile acid forms tested against the various antisera have been published previously.[9]

Following addition of purified tritium-labeled bile acids, antibody-bound and free bile acids were separated using polyethylene glycol and the "free" counts from the supernate decanted into scintillation vials containing liquid scintillation counting cocktail. Radioactivity was determined and the concentration of the individual bile acids expressed as micromoles of glycine

From the Departments of Pathology and Pediatrics, Milton S. Hershey Medical Center, Pennsylvania State University, Hershey (Dr Demers), and the Division of Gastroenterology, Children's Memorial Hospital, Chicago (Dr Lloyd-Still).

Read in part before the American Pediatric Society/Society for Pediatric Research, San Francisco, April 28, 1977.

Reprint requests to Milton S. Hershey Medical Center, Hershey, PA 17033 (Dr Demers).

Table 1.—Clinical Details of 14 Infants With Intractable Diarrhea

Patient/ Age, Mo	Intestinal Biopsy*	Mono-saccharide Intolerance	Culture of Duodenum, Organisms/ml	Serum Albumin, g/dl	Total Serum Bilirubin mg/dl	SGOT, Units	Pro-thrombin Time, sec	Cholyl-glycine, μM	Chenodeoxy-cholylglycine, μM
1/1	III	Yes	$>10^6$ *Pseudomonas* $>10^6$ *E coli*	3.3	0.4	53	11.5	4.85	1.82
2†/3	I	Yes	$>10^4$ *Candida*	2.3	1.0	27	12.4	7.22	1.34
3/18	II	No	Negative	...	...	...	12.2	7.82	1.62
4/12	II	No	Negative	...	...	...	...	1.46	2.16
5†/3	IV	Yes	Negative	2.0	...	29	13.0	0.26	0.06
6†/21	III	Yes	$>10^6$ *Clostridia*	2.0	0.7	...	14.0	0.83	11.7
7/2	...	No	...	3.2	...	...	13.1	1.83	0.3
8‡/1	...	Yes	...	2.7	2.3	34	16.5	0.26	1.58
9/24	III	Yes	$>10^4$ *S aureus*	3.4	...	28	15.0	0.89	2.50
10/1	...	Yes	$>10^4$ *Candida*	3.4	...	19	...	2.2	7.2
11†/3	...	Yes	...	...	...	32	...	2.44	1.5
12‡/3	I	Yes	10^4 *Candida*	3.5	0.8	117	...	1.2	1.1
13‡/2	III	Yes	$>10^5$ *E coli*	1.8	0.9	36	13.3	4.8	3.0
14‡/3	...	Yes	10^4 *Candida*	2.6	0.5	140	...	1.4	2.8
Normal infants	...	...	$>10^4$ of fecal type	3.7-5.2	0.3-0.8	8-31	11.0	0.05-0.34	0.02-0.61

*I indicates normal; IV, total villus atrophy.[20]
†Peripheral alimentation for three to seven weeks.
‡Elemental diet for three to six weeks.

Table 2.—Serum Concentrations (Mean ± SEM) of Four Bile Acids

	Controls		Patients With Inflammatory Bowel Disease* (N = 15)	Patients With Protracted Diarrhea (N = 14)
	Neonates* (N = 34)	Children† (N = 18)		
Cholylglycine, μmole/liter	0.61 ± 0.03	0.15 ± 0.02	0.39 ± 0.09	2.68 ± 0.67‡
Chenodeoxycholylglycine, μmole/liter	0.80 ± 0.07	0.13 ± 0.03	0.46 ± 0.17	2.76 ± 0.82‡
Deoxycholylglycine, μmole/liter	0.11 ± 0.01	0.04 ± 0.01	...	0.15 ± 0.05
Sulfolithocholylglycine, μmole/liter	0.20 ± 0.02	0.12 ± 0.01	0.35 ± 0.06	0.31 ± 0.09

*Two hours post-prandially.
†Fasting.
‡Significant at $P < .05$ from the control group.

Table 3.—Concentrations (Mean ± SEM) of Two Serum Bile Acids in Patients With Protracted Diarrhea Treated by Different Regimens

	No. of Patients	Cholylglycine, μmole/Liter	Chenodeoxycholylglycine, μmole/Liter
Elemental diet	4	2.07 ± 0.91	2.35 ± 0.43
Intravenous alimentation	4	2.69 ± 1.58	3.65 ± 2.70
Oral/intravenous	6	3.07 ± 1.13	2.45 ± 0.98

conjugated bile acids per liter of serum. Student's t test was used to assess statistical significance.

Clinical Data

Fourteen patients with intractable diarrhea of infancy were studied (Table 1). None were breast-fed. Eleven infants had secondary monosaccharide intolerance. Five patients had pathogenic microorganisms isolated from their stools, including enteropathogenic *Escherichia coli*, *Salmonella*, and *Staphylococcus aureus*. Culture of the upper intestine was performed in 11 patients; three had fecal flora and five *Candida albicans*.[19] Intestinal biopsy specimens were obtained on nine infants, seven of which showed varying degrees of villus atrophy. There were raised serum bilirubin levels in two of seven patients, and SGOT level was mildly raised in six of ten patients. Alkaline phosphatase value was raised in five of seven patients. Prothrombin time was prolonged in eight of nine patients. Serum albumin concentration was low in all 11 patients in whom it was measured.

Therapy included intravenous peripheral alimentation (average duration, six weeks) in four patients, constant-infusion intragastric elemental diet (average duration, four weeks) in four patients, and various intravenous and oral dietary manipulations in the remaining six patients (none of these received parenteral alimentation or elemental diet).

RESULTS

Eighteen children (aged 1 to 12 years) without known hepatic disease served as controls. Serum was taken after a six-hour fast. Control values in 34 neonates taken two hours postprandially are also given for comparison. The results of serum bile acid concentrations in the 14 patients with protracted diarrhea are shown in Table 2. Serum bile acid concentrations showed significant increases over controls for cholylglycine ($P < .001$) (Figure) and chenodeoxycholylglycine ($P < .01$). To see wheth-

er the raised levels of cholylglycine and chenodeoxycholylglycine were related to specific therapy, we compared the mean values in relation to therapy (Table 3). No significant differences could be found between the levels of the primary bile acids with elemental diet, intravenous alimentation, or oral intravenous therapy. The serum bile acid values for 15 children (aged 4 to 15 years) with chronic inflammatory bowel disease (nine with ulcerative colitis, six with Crohn's disease) are also included for comparison. These samples were taken two hours postprandially and are in the normal range for these values.[11]

COMMENT

This study demonstrates significant increases in serum levels of cholylglycine and chenodeoxycholylglycine in infants with the protracted diarrhea syndrome. There were no significant differences in the serum bile acid levels in relation to treatment with either intravenous alimentation, constant-infusion elemental diet, or other oral and intravenous manipulations. Although it could be argued that constant-infusion elemental diet and parenteral alimentation would tend to raise the levels of serum bile acids, the maximum level for cholylglycine and chenodeoxycholylglycine postprandially in normal patients[11] is significantly less than in our infants with intractable diarrhea. Moreover, the serum bile acid levels were quite distinct from those in 15 children with chronic inflammatory bowel disease. Thus, the increased serum bile acid levels are probably related to the syndrome of intractable diarrhea in infancy as well as being an effect of therapy.

Abnormal liver function values were reported previously in infants with intractable diarrhea,[1] but since they reverted to normal after therapy was stopped, they were ascribed to the effects of the intravenous alimentation. Gunn et al[7] recently reported their experience in the treatment of 34 infants with intractable diarrhea. SGOT levels were elevated in 80% of the patients at the time of admission, increased further in 82% when parenteral nutrition was begun, but decreased to normal prior to discharge. Liver biopsy specimens in seven patients showed eosinophilia, increased pigment in the Kupffer cells, and lymphocytosis in the portal tract.

The significance of these findings is poorly understood, but several factors may be involved. Bile salt synthesis and excretion are under feedback control.[12] Excess fecal bile acid loss may alter the feedback mechanisms controlling liver bile acid formation, resulting in increased primary bile salt synthesis. Bile salts are also involved in host defense mechanisms in the gastrointestinal tract, and decreased concentrations of bile acids in the intestinal lumen may lead to abnormal absorption of endotoxin.[13] Cooperstock and Riegle[14] reported that 35% of infants with major gastrointestinal disturbances had evidence of plasma endotoxin-like activity as measured by the limulus gelation microtechnique. *Escherichia coli* endotoxin causes decreased hepatocyte function in the rat, leading to cholestasis.[15] Similar findings have been reported in the premature infant.[16] Lastly, alterations in the levels of amino acids in serum may lead to hepatic dysfunction with increased serum bile acid levels.[17] Changes in serum amino acid levels have been demonstrated in patients receiving parenteral nutrition[18] and constant-infusion elemental diets.[19] It is interesting to note that protein deficiency was the most consistent biochemical abnormality in our infants with protracted diarrhea. However, plasma amino acid levels were not determined in our infants.

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Cerebellar Medulloblastoma

An Analysis of Four Cases of Extraneural Metastasis

Eugene R. Schnitzler, MD; Marcia J. S. Richards, MD; Raymond W. M. Chun, MD

• In four of 28 patients (14%) with medulloblastoma who were treated at the University of Wisconsin, Madison, over a 20-year period, extraneural metastases developed. In an effort to delineate the causal factors involved in extraneural metastases, salient features of patients with metastases and without metastases were compared. Suboccipital craniectomy, radiation therapy, and patient longevity were not well correlated with metastases. However, subarachnoid tumor spread was a consistent precursor. A ventriculoatrial shunt may have been a factor in one patient and a serious infection that preceded diffuse metastasis may have been a factor in another patient. Half of the patients with metastases were found to have the desmoplastic variety of medulloblastoma while only one of 24 patients without metastases had this tumor type.

(*Am J Dis Child* 132:1004-1008, 1978)

Medulloblastoma, a highly malignant tumor of the cerebellum, accounts for one fifth of the intracranial neoplasms in the pediatric age group.[1] The tumor is believed to be derived from the medulloblast, an embryonal, bipotential cell, capable of maturation along either glial or neural cell lines. While medulloblastomas are known to frequently spread along CSF pathways, metastasis of this tumor outside of the CNS is considered very unusual.[2]

A review of the literature shows approximately 60 reported cases of patients who had extraneural spread of medulloblastoma.[3,4] The conditions predisposing to metastases are obscure and they remain the subject of speculation. Factors cited include the following: initial surgical intervention, radiation therapy, subarachnoid tumor spread, patient longevity, shunt procedures, and tumor histology.[5,6,7]

There have been 28 patients with medulloblastoma who were treated by the Radiation Oncology Department of the University of Wisconsin at Madison during the 20-year period from 1957 to 1976. (This figure does not include those patients who died during the operative period before receiving radiation therapy.) In four of these patients (14%) extraneural metastasis developed. This incidence is unusually high and warrants investigation. This article will review the cases of four patients who had extraaxial metastases and compare their clinical features with those of the patients who had medulloblastoma without metastasis.

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Reprint requests to Departments of Neurology and Pediatrics, 1300 University Ave, Madison, WI 53706 (Dr Schnitzler).

REPORT OF CASES

Case 1.—A 5-year-old girl was admitted to another hospital in 1966 with a three-week history of vomiting and abdominal pain. After hospitalization, progressive lethargy, truncal ataxia, nystagmus, and hypotonia developed. A pneumoencephalogram (PEG) and arteriogram showed evidence of a posterior fossa mass. A suboccipital craniectomy was performed with removal of a firm homogenous tumor arising from the roof of the fourth ventricle. Results of a microscopic examination confirmed a medulloblastoma. Postoperatively, she received 3,300 rads to the cranium and 2,850 rads to the spinal axis. Her clinical status improved greatly. Ten months later, back pain and a gait disturbance developed. A myelogram showed a mass at L-1 to L-3. This was irradiated with 1,350 rads, with apparent resolution.

Four years later, she began to complain of pain of the left thigh and difficulty walking. Results of a neurological examination showed a decrease in pain sensation on the medial aspect of the left thigh, absence of the patellar reflex in the left knee, and weakness of the left hip. A myelogram showed an incomplete block at T-12 to L-1 and a shallow filling defect at L-4 to L-5. A laminectomy from T-11 to L-2

showed arachnoiditis. The scar tissue was partially excised but postoperatively, her condition did not improve.

One month later, results of an examination showed a large mass above the left iliac crest. An intravenous (IV) pyelogram showed nonvisualization of the left kidney and a tortuous ureter on the right side displaced by a mass (Figure). A biopsy specimen of the mass was read as metastatic medulloblastoma. The patient was given an intraarterial dactinomycin drip for two weeks and she simultaneously received 4,500 rads to the mass. The tumor responded with substantial shrinkage. She was given a prolonged course of vincristine sulfate with noticeable improvement in her strength and in her ability to walk. Eight months later, the family moved to another city. However, the patient was known to be alive and receiving chemotherapy 4½ years after completion of irradiation for the metastasis.

CASE 2.—A 3½-year-old boy was admitted in 1974 with a four-week history of vomiting and ataxia. Brain scan, arteriogram, and PEG showed a midline posterior fossa tumor. He underwent suboccipital craniectomy with subtotal resection of a medulloblastoma from the fourth ventricle. His postoperative course was complicated by a pseudomeningocele and a staphylococcal ventriculitis that responded to methicillin sodium. He received 4,000 rads to the cranium, a 1,000-rad boost to the posterior fossa, and 3,500 rads to the spinal axis.

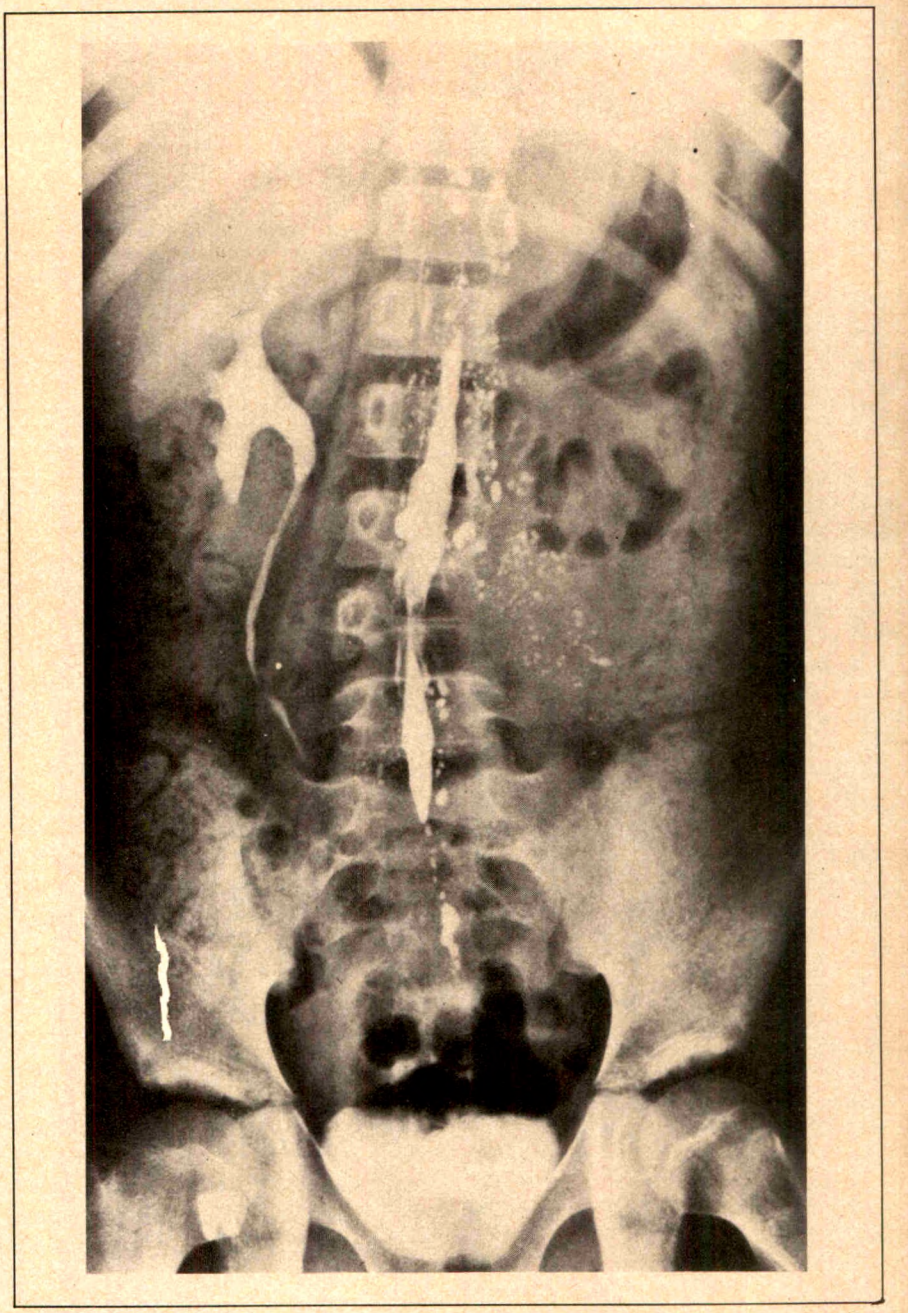
Two months later, the patient had a recurrence of the ventriculitis. A Rickham reservoir was inserted and he was given IV and intraventricular methicillin for two weeks.

Six months later, he was readmitted with lymphadenopathy, edema of the right upper extremity, and bleeding from the lips. A liver scan showed multiple areas of decreased uptake. Biopsy specimens of the liver and the lymph node showed metastatic medulloblastoma. Chemotherapy was refused and the patient's condition progressively worsened. He died several weeks later.

Autopsy showed extensive metastases to the pleura, the pericardium, the gallbladder serosa, the liver, and multiple lymph nodes. There was also evidence of extradural tumor extension in the lumbosacral spine. Multiple tumor foci in the brain parenchyma were found. A diffuse subacute bacterial cerebrospinal leptomeningitis and ventriculitis were also noted.

CASE 3.—A 3-year-old boy was admitted in 1965 with a six-week history of frequent falling and unsteady gait. Results of an examination showed truncal ataxia, hypotonia, bilateral nystagmus, and mild papilledema. Skull roentgenograms showed spreading of the cranial sutures and a ventriculogram showed a mass in the fourth ventricle. A suboccipital craniectomy with complete resection of tumor was done. Results of a histological examination confirmed a medulloblastoma. After surgery, he received radiation therapy totaling 4,120 rads to the cranium and 4,094 rads to the spinal axis. A Pudenz shunt was placed two months after surgery to control increased intracranial pressure.

He was readmitted five months later with vomiting and lethargy and he quickly lapsed into a coma. A biopsy specimen of a large cervical lymph node showed metastatic medulloblastoma. He received three doses of vincristine sulfate, 1 mg, at one-week intervals. Although there was noticeable shrinkage of the cervical node, his general condition did not improve and he died six weeks later.



Intravenous pyelogram of patient 1 showing nonfunctioning left kidney and large midabdominal mass on the left side. There is lateral deviation of ureter on the right side secondary to mass effect. Residual contrast material from myelogram shows left extradural defect at L-4. There is also destruction of left lateral and anterior aspects of L-4 vertebral body and of left pedicle.

Comparison of Patients With Medulloblastoma With Metastases and Without Metastases

	Median Age at Diagnosis, yr	Mean Survival, mo	No. of Patients					
			Suboccipital Craniectomy	Above-Average Radiation Therapy: > 5,500 Rads to the Brain; > 4,000 Rads to the Spine	Evidence of Subarachnoid Spread	Additional Surgery	Serious Complicating Infections	Desmoplastic Medulloblastoma
Patients with metastases (N = 4)	4 (range, 3-10)	36 (range, 7-115)	4	1	4	4	1	2
Patients without metastases (N = 24)	8.5 (range, 3-60)	47 (range, 5-225)	23	3	7	11	4	1

Autopsy showed a well-circumscribed nodular tumor mass in the posterior vermis that was microscopically consistent with the desmoplastic variety of medulloblastoma. Leptomeningeal spread of the tumor was noted, particularly around the foramen magnum and the base of the brain.

CASE 4.—A 9-year-old boy entered the hospital in 1963 with a four-month history of headaches and vomiting. (This case has been previously reported as an example of extracranial metastasis via the lymphatic and vascular channels.[8]) An examination showed papilledema and bilateral sixth nerve weakness. He also had generalized hypotonia and mild dysmetria on finger-to-nose testing. Pneumoencephalogram and ventriculogram showed a posterior fossa mass.

A suboccipital craniectomy was performed and a tumor infiltrating the roof of the fourth ventricle and the cerebellum was found. Results of a microscopic examination confirmed a medulloblastoma. This was partially resected and the patient received radiation therapy consisting of 4,000 rads to the posterior fossa, 2,600 rads to the dorsal spine, and 2,250 rads to the lumbar spine.

He was readmitted seven months later because of severe truncal ataxia. Roentgenograms showed osteoblastic metastasis in the lumbar vertebral bodies, pelvis, ribs, sternum, femurs, and humeri. He received a five-day course of IV dactinomycin and 2,400 rads to the upper dorsal spine. This resulted in some degree of improvement in his gait and balance. Four months later, a ventriculoatrial shunt was placed because of persistent signs of increased intracranial pressure. In spite of this, he died after a difficult hospital course. At autopsy, desmoplastic medulloblastoma was found over the surfaces of the cerebellum, the cerebrum, the brain stem, and the dorsal spinal cord. In addition, sections of the skull and thoracic and lumbar vertebrae showed infiltrating medulloblastoma.

RESULTS

Clinical information regarding the factors most frequently cited as pertinent to metastasis was reviewed for each of our 28 patients. A summary of these data is given in the Table that compares patients with metastases with patients without metastases. The median age of diagnosis for the patients with metastases was four years. The median age at diagnosis for the patients without metastases was 8½ years. The mean survival time for patients with metastases was 36 months (range, seven to 115 months). The mean survival time for patients without metastases was 47 months (range, five to 225 months). There appears to be no significant difference between these figures and those of other reported series.[1,9]

All four of the group with metastases underwent suboccipital craniectomy and 23 of 24 patients without metastases underwent this procedure initially as well. Similarly, virtually all the patients in both groups had radiation therapy to the tumor and usually also to the brain and spinal axis. Only one patient in the group with metastases (case 1) may have received a slightly higher-than-average cumulative dose of radiation to the spine prior to the development of extraneural metastasis. Three patients without metastases received above-average cumulative irradiation.

Clinical or autopsy evidence of tumor spread along subarachnoid channels was found in all four patients with metastases. Seven of the 24 patients without metastases showed similar evidence of subarachnoid spread.

Additional surgery in this series usually refers to shunting procedures. Other operations included in this category were laminectomies and burr holes. All four patients with metastases had additional surgery: two had shunts, one a Rickham reservoir, and one a laminectomy. Eleven of the 24 patients without metastases had additional operative procedures. These included ten patients with shunts, several requiring multiple revisions. One patient had bilateral parietal burr holes three days prior to suboccipital craniectomy. Another patient without metastases required a second suboccipital craniectomy for local recurrence and several shunt procedures.

Serious infection (ventriculitis) occurred in the patient in whom the most widespread metastases subsequently developed (case 2). Four patients without metastases also had complicating infections. Two of the four patients with metastases had the desmoplastic variety of medulloblastoma. In contrast, of 24 patients without metastases, only one had the desmoplastic variant.

COMMENT

Appropriate criteria for making the diagnosis of extraneural metastasis of CNS tumors is subject to debate. The pathological conditions most frequently considered are those first proposed by Weiss[10] in 1955. These are as follows: (1) having the presence of a single histologically characteristic tumor of the CNS, (2) having the patient's clinical symptoms shown to be due to the tumor, (3) having a complete autopsy done to rule out the

possibility of another primary tumor, and (4) having a morphology of the CNS tumor and the metastasis that is identical except for differences in degree of anaplasia. Three of the cases of patients with metastases met these requirements for diagnosis of extraneural tumor spread. The patient in case 1 survived and therefore was not an appropriate subject for comparison.

As Drachman et al[5] have emphasized, for an intracranial tumor to metastasize, two prerequisites must be met. First, the tumor must gain access to the blood or to the lymphatic channels. Second, tumor emboli must lodge in distant sites that will be conducive to their growth. Thus, extraneural metastases from medulloblastoma are usually found in bone and lymph nodes. (The lungs and pleura are spared unless a shunt is implicated.) Factors given in the Table are believed to enhance the metastatic process. However, the actual mechanisms involved are not understood and clear cause and effect relationships have not been shown.

Paterson[11] reported three cases on which autopsy was done in which metastatic medulloblastoma with dural penetration of the operative site was found. She hypothesized that the initial surgical intervention and/or radiation therapy broke down the normally present CNS barriers to metastasis. Miyake and associates[12] came to a similar conclusion. In contrast, Kessler et al[13] found no association between scalp wound contamination and lymphatic metastasis. Moreover, both Drachman[5] and Paterson[11] acknowledged that since almost all medulloblastomas are surgically explored, the possible causal role of suboccipital craniectomy could not be determined. Our data tend to support this contention. Suboccipital craniectomy was a virtually constant factor in both patients with and without metastases. Autopsy was done on three cases in which metastases had been present and of these, two showed definite microscopic tumor invasion of tissues at the operative site. Detailed autopsy information was available on four cases in which there was no metastasis, and no wound invasion by tumor was found in them.

The possibility that radiation therapy enhances metastasis has been suggested.[5] However, radiotherapy has improved the survival rate of patients with medulloblastoma without any apparent predisposition to metastatic lesions.[1,14] Radiation was a constant part of the therapeutic regimen of patients with and without metastases in this series. No evidence of a causal relationship between radiation therapy and subsequent metastasis was seen.

Although it has been speculated that prolonged survival of the patient may increase the probability of metastasis, Drachman's summary[5] of the literature does not support this contention. However, a review by Kessler et al[13] of 53 patients with metastasized medulloblastoma found 39 of them surviving more than one year. In our group with metastases, cases 2, 3, and 4 had rapid downhill courses with survivals of 8, 7, and 16 months, respectively. In case 1 a metastatic abdominal mass developed five years after the original tumor resection. In contrast, the average survival of the patients without metastases was 47 months. Thus, metastasis was not a consistent factor associated with longevity and instead seemed to lead to a shortened survival.

Seeding of subarachnoid pathways was confirmed at autopsy in cases 2, 3, and 4. Although not histologically proved, the history and roentgenographic studies suggest that seeding occurred in case 1 with metastases as well. A review of the cases without metastases showed definite autopsy, roentgenographic, or clinical evidence of subarachnoid spread in seven of 24 patients (29%). This figure is consistent with the incidence of 33% for subarachnoid spread of medulloblastoma observed by others.[15] If a high incidence of subarachnoid seeding continues to be found in patients with metastasis, it would imply that this process is an important factor in extraneural tumor spread.

In recent years, there has been much discussion regarding the possible role of shunts in enhancing the metastasis of medulloblastoma. Makeever and King[6] first reported this complication in an infant who had a ventriculovenous shunt. Kessler et al[13] described another patient in whom a lumboperitoneal shunt was implicated. Hoffman et al[16] reported on a series of 41 patients with medulloblastoma who were treated with a ventriculoperitoneal shunt prior to tumor resection. Generalized systemic metastases developed in four patients with tumor implants found in the peritoneum. These authors suggested that the spread of tumor cells through shunts could be prevented by means of a permeable membrane filter (Millipore).

In the present series, the shunting procedure could have predisposed to metastasis only in patient 3. In this patient cervical lymph node metastases developed two months after a ventriculoatrial shunt was inserted. It is true that patient 4 also had a Pudenz shunt procedure. However, metastases were evident roentgenographically in this patient prior to the shunt surgery. Patient 2 had a Rickham reservoir placed for treatment of ventriculitis. However, this device does not carry CSF to other body sites and thus should not be considered in the same category as a shunt.

In the group without metastases, ten of 24 patients underwent shunting procedures. Several of these patients required multiple shunt revisions. When patients both with and without metastases are considered together, 12 patients received shunts, and an 8% incidence (one in 12) of shunt-related metastasis was observed. This finding is consistent with the observation of Hoffman et al[16] of a 10% incidence of shunt metastasis.

Additional surgery in patient 1 consisted of a laminectomy of T-11 to L-2. A few months later, an abdominal mass was noted. However, retrospective analysis of this patient suggests that the metastatic tumor was already present in the retroperitoneal space prior to laminectomy.

In the case of patient 2, additional procedures consisted only of freqent lumbar punctures and insertion of the Rickham reservoir for ventriculitis. It is difficult to postulate of a causal relationship between these measures and this patient's overwhelming

metastasis. Perhaps the ventriculitis itself led to a breakdown of normal defense mechanisms with the resultant hematogenous spread of the tumor. Patient 2 was the only one in whom serious infection could be implicated. In contrast, two patients without metastases had CNS infection or sepsis, and two others had sepsis in the terminal stage of their course.

In the present series, two patients with metastases (cases 3 and 4) were found to have the desmoplastic variety of medulloblastoma. There is considerable argument in the literature that these tumors are not truly medulloblastomas but rather so-called circumscribed cerebellar sarcomas.[17] However, a comprehensive review of this controversy by Rubinstein and Northfield[7] concluded that these tumors were in fact variants of medulloblastoma. Their use of the term "desmoplastic medulloblastoma" referred to tumors that tended to arise more frequently in young adults with localization more laterally in the cerebellum. Histologically, the desmoplastic variant was characterized by an abundance of reticulin fiber formation.

Zimmerman et al[18] suggest that this type of medulloblastoma may be more prone to extra-axial metastasis. Rubinstein and Northfield[7] confirmed that two of three of their patients with metastasis had the desmoplastic type of tumor. They speculated that the tendency of desmoplastic cells to stimulate growth of connective tissue might enhance tumor spread at distant locations. They also postulated that the allegedly longer survival of desmoplastic tumor cases might increase the likelihood of metastases.

The present review neither confirms nor denies the contention that desmoplastic medulloblastomas are more metastatic than their classical counterparts. The two varieties were equally represented among the patients with metastases. In the group without metastases only one patient was noted to have a desmoplastic tumor. Although the 50% incidence of desmoplastic medulloblastoma in the group with metastases is suggestive of a greater tendency toward metastasis, the small number of patients prevents a definitive conclusion.

Identification of the patient with medulloblastoma with an increased risk of extraneural metastasis is difficult. Suboccipital craniectomy, radiation therapy, and patient longevity did not appear to predispose to metastases in this series. However, multiple factors, including subarachnoid spread, infection, shunt procedures, and tumor histology, may play a role in the pathogenesis of this process. The problem has practical implications since recent studies indicate that extraneural metastases of this tumor are sensitive to chemotherapy.[19,20,21] Clinical vigilance is imperative if this complication is to be recognized and treated early.

Karen Magnuson provided secretarial help in preparing the manuscript.

Nonproprietary Names and Trademarks of Drugs

Dactinomycin—*Cosmegen.*
Vincristine sulfate—*Oncovin.*

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Takayasu's Arteritis Associated With Glomerulonephritis

A Case Report

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• Takayasu's disease is a nonspecific arteritis of unknown cause with predilection for the aortic arch and its branches; approximately 20% of those affected are children or adolescents, predominantly females.

The purpose of this article is to report the case of a young girl in which the mode of presentation was microscopic hematuria and proteinuria. Subsequently, aortic valvular insufficiency developed and there was evidence of aortitis in the thoracic and abdominal aorta, as well as in the arch. All functional and anatomical cardiac derangements were documented by ultrasound and angiocardiography. Renal biopsies showed progressive glomerular involvement characterized by focal and segmental glomerulonephritis. It is postulated that a common immunologic mechanism was responsible for the aortic and glomerular lesions.

(*Am J Dis Child* 132:1009-1013, 1978)

Takayasu's disease (TD) is a nonspecific arteritis of unknown cause, affecting predominantly young women, and producing inflammation and obliteration of large and medium size arteries. A striking predilection for the aortic arch and its branches is characteristic ("pulseless disease").[1,2] In the literature, there are several extensive reviews of the clinical manifestations and pathologic findings in this disease.[3-6] Approximately 20% of those affected are children or adolescents.[4]

Classically, TD has been associated with ocular, cerebral, and systemic manifestations. Renal involvement usually has included vascular hypertension and other ischemic renal complications.[7-10] In a few cases, a history of glomerulonephritis has been found.[11] However, to our knowledge, there has been no report of progressive glomerular involvement associated with TD. The purpose of this article is to report one such case in a young woman with asymptomatic microscopic hematuria and proteinuria. Extensive involvement of the aorta and its branches was documented by echocardiogram and aortography.

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REPORT OF A CASE

A 15-year-old girl was found to have microscopic hematuria and mild proteinuria in a routine urinalysis during September 1975. In November 1975, she had a complete evaluation at the University of Miami–Jackson Memorial Medical Center. Physical examination showed an active, slender girl in no acute distress. Blood pressure was 100/70 mm Hg. Head, eyes, ears, nose, and throat were unremarkable; lungs were clear; no heart murmurs were found. The abdomen was within normal limits. The following laboratory values were found: decreased hemoglobin, 8.8 g/dl; hematocrit, 29%; elevated sedimentation rate, 116 mm/hr; serum IgG, greater than 2,000 mg/dl; and serum IgA, 950 mg/dl. Other test findings, including creatinine clearance, serum electrolytes, BUN, and total serum complement were all within normal limits; antinuclear antibodies and lupus erythematosus cell preparation were negative. Intravenous pyelogram and cystourethrogram were normal. Renal biopsy specimen showed only presence of RBCs in the tubules and normal glomeruli

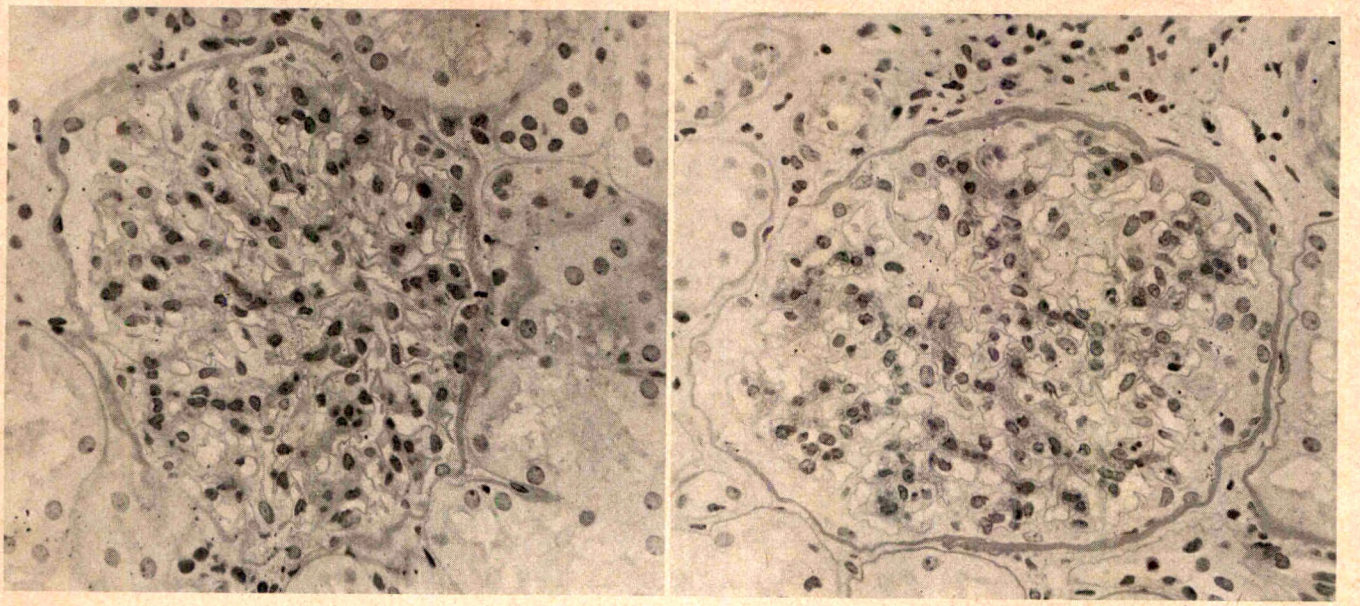


Fig 1.—Left, First renal biopsy specimen. Glomerulus exhibiting normal configuration and cellularity (PAS stain, original magnification ×450). Right, Second renal biopsy specimen. Glomerulus exhibiting diffuse mesangial proliferation and increase in mesangial matrix (PAS stain, original magnification ×450).



Fig 2.—Second renal biopsy specimen. Section stained with fluorescent labeled antihuman M immunoglobulin showing mesangial deposits of IgM (original magnification ×325).

by light (eight glomeruli) and electron microscopy (one glomerulus, Fig 1, left). Immunofluorescence could not be performed since no glomeruli were found in the available material.

She was seen again in November 1976, with general malaise, worsening of hematuria (sometimes gross), persistent anemia, and elevated sedimentation rate. Physical examination on admission showed a somewhat pale, thin girl in no acute distress. Heart rate was 82 beats per minute; respirations were 18 per minute; blood pressure in the right arm was unobtainable, left arm 112/60 mm Hg, right leg 120/69 mm Hg, and left leg 115/65 mm Hg. Right radial and brachial pulses were absent, whereas the left brachial and both carotid and femoral pulses seemed within normal limits. Cardiac apex was within normal limits; first and second sounds were normal and there were no extra sounds. There was a grade II/VI early, high frequency, "indecrescendo," diastolic murmur at the aortic arch and a grade II/VI systolic ejection murmur at the suprasternal notch area with radiation to both carotid arteries. A systolic ejection murmur also was found in both paraumbilical areas. No skin rashes, hepatomegaly, or splenomegaly were present. Examination of the CNS and retina were unremarkable. Repeated temperature determinations were normal.

Laboratory findings showed normal renal function with creatinine clearance of 93 ml/min/1.73 sq m. Urinalyses revealed gross hematuria and mild proteinuria (30 to 100 mg/dl), but no casts. The second renal biopsy specimen showed definite changes compared with the first one, including increase in mesangial matrix, mesangial proliferation, and capsular sclerosis by light microscopy (12/21 glomeruli, Fig 1, right). Electron microscopy demonstrated abundant mesangial electron dense deposits (located against the nonfiltering portion of the basement membrane and in the mesangial matrix) in the one glomerulus studied. Immunofluorescence showed 1+ mesangial deposits of IgG, IgA, IgM, C3, C4, and properdin in the six glomeruli studied (Fig 2). The pathologic diagnosis was focal and segmental mesangial glomerulonephritis.

The ECG showed sinus rhythm, axis deviation of the QRS complexes of about plus 55°, normal atrial forces, and left ventricular forces at the upper limits of normal. Cardiac size by chest roentgenogram was within normal limits; there was a prominent aortic knob with calcification (Fig 3). Echocardiogram revealed increased aortic root dimension but normal left atrium, left ventricular dimensions and wall thickness, and normal mitral valve motion (Fig 4). Aortography demonstrated a dilated ascending aorta, mild aortic insufficiency, no abnormalities in the main right or left coronary arteries, diffuse and multiple obstructive lesions of the aortic wall and its branches, aneurysm of the right brachiocephalic trunk, and diffuse narrowing of the subclavian artery. There was absence of opacification of both renal arteries and of the superior mesenteric artery that seemed to be occluded. However, both kidneys were well visualized with the right side appearing earlier (Fig 5). Systolic pressures in the ascending aorta (190/70 mm Hg) and the left ventricle were elevated.

Other studies included protein electrophoresis with a decreased serum albumin level (3 g/dl), hypergammaglobulinemia (2.12 g/dl), and increased $\alpha 1$ and $\alpha 2$ globulins and haptoglobin (480 mg/dl) levels. Several complement levels (C3 and C4) were normal. Serum immunoglobulin levels were as follows: IgG, 3,800 mg/dl (normal range, 408 to 1,788 mg/dl); IgA, 1,000 mg/dl (normal range, 64 to 544 mg/dl); and IgM, 190 mg/dl (normal range, 49 to 355 mg/dl). The following tests were negative: Coombs, antistreptolysin O titer, antihyaluronidase titer, Australia antigen, antinu-

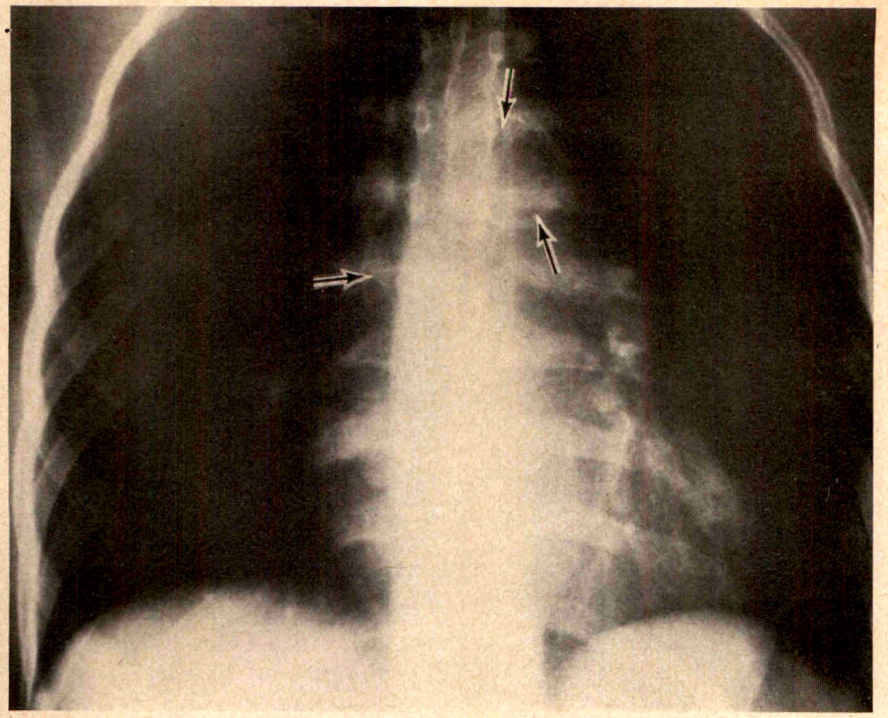


Fig 3.—Chest roentgenogram showing aortic wall calcification (arrows).

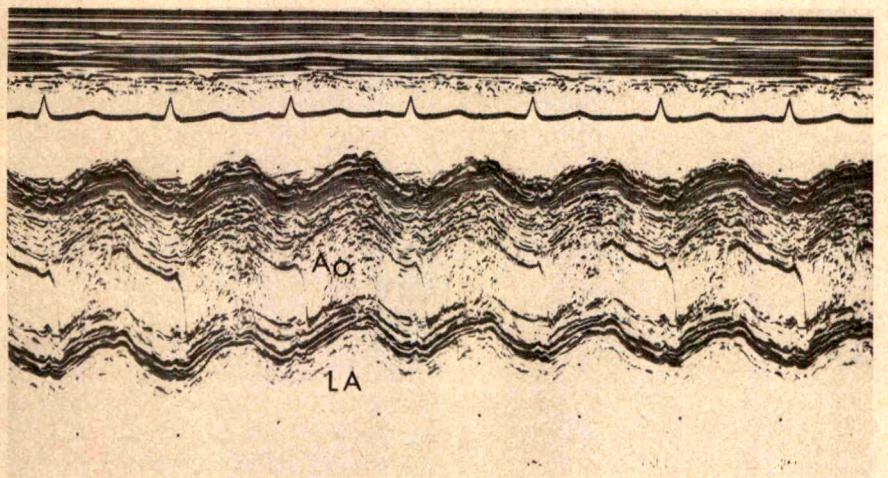


Fig 4.—Echocardiogram of aortic root at level of aortic valve demonstrating increased aortic root diameter of 32.8 mm (normal, 19 to 27 mm).

clear antibodies, lupus erythmatosus, latex fixation, VDRL, blood cultures (nine times), skin purified protein derivative, and serum cryoglobulins.

Bilateral renal vein and peripheral blood renin levels obtained while patient was in a supine position and without sodium restriction or diuretic administration were as follows: right, 1.13 ng/ml/hr; left, 1.50 ng/ml/hr; and peripheral, 0.93 ng/ml/hr (normal range, 0.3 to 0.7 ng/ml/hr). Temporal artery biopsy specimen was considered normal. The aforementioned findings were consistent with the clinical diagnosis of nonspecific arteritis of the aorta.

In April 1977, the patient received triple therapy with prednisone, azathioprine, and cyclophosphamide, 1 mg/kg/day of each. After ten months of therapy, the systemic manifestations of her disease improved considerably. Anemia was corrected, sedimentation rate had decreased, and serum immunoglobulins were within normal limits. Urine sediment values improved and creatinine clearance remains normal. Cardiovascular manifestations also have improved; there is now detectable pulse and blood pressure on her right arm and the diastolic murmur is almost undetectable.

COMMENT

To date, there are more than 100 detailed reports of autopsy material of patients with TD from various parts of the world.[12] A review of the literature showed reports of up to 500 clinical cases, but when strict diagnostic criteria are employed only two thirds of these can be classified as TD.[13] A large number of TD cases reported have been from Japan. Takayasu disease has been considered to be rare in the United States; however, recent investigations indicate that it may be more common than has been suspected.[12,14]

Based on the extent and localization of lesions by aortography, Nakao et al[3] described the disease as having three main categories: first, the classical type in which the aortic arch and the brachiocephalic vessels are exclusively involved; second, the extensive type in which the entire aorta and its branches are diseased; and third, a type that may be localized or extensive but with the ascending aorta and aortic arch radiologically normal.

The diagnosis in the patient reported here was suspected clinically, based on undetectable pulse and blood pressure in the right arm, associated with aortic insufficiency. Helpful tools in this diagnosis were a dilated aortic root found by echocardiography, calcification of the aortic arch found in the chest roentgenogram, abnormal serum protein electrophoresis and serum immunoglobulins, persistent anemia, and elevated sedimentation rate. Angiocardiography confirmed the diagnosis. Other types of aortic arch syndromes, including atherosclerosis and syphilis, were ruled out. The presence of a normal temporal artery biopsy specimen does not exclude TD since spotty arterial involvement usually is present in this and related diseases.[15]

It has been reported that 20% of the population affected with TD is younger than 19 years of age.[4] Sex distribution at all ages shows a definite predominance of females (88%).[4] Although the abdominal aorta seems to be the most common site of involvement in children,[16] our patient presented with a combination of lesions,

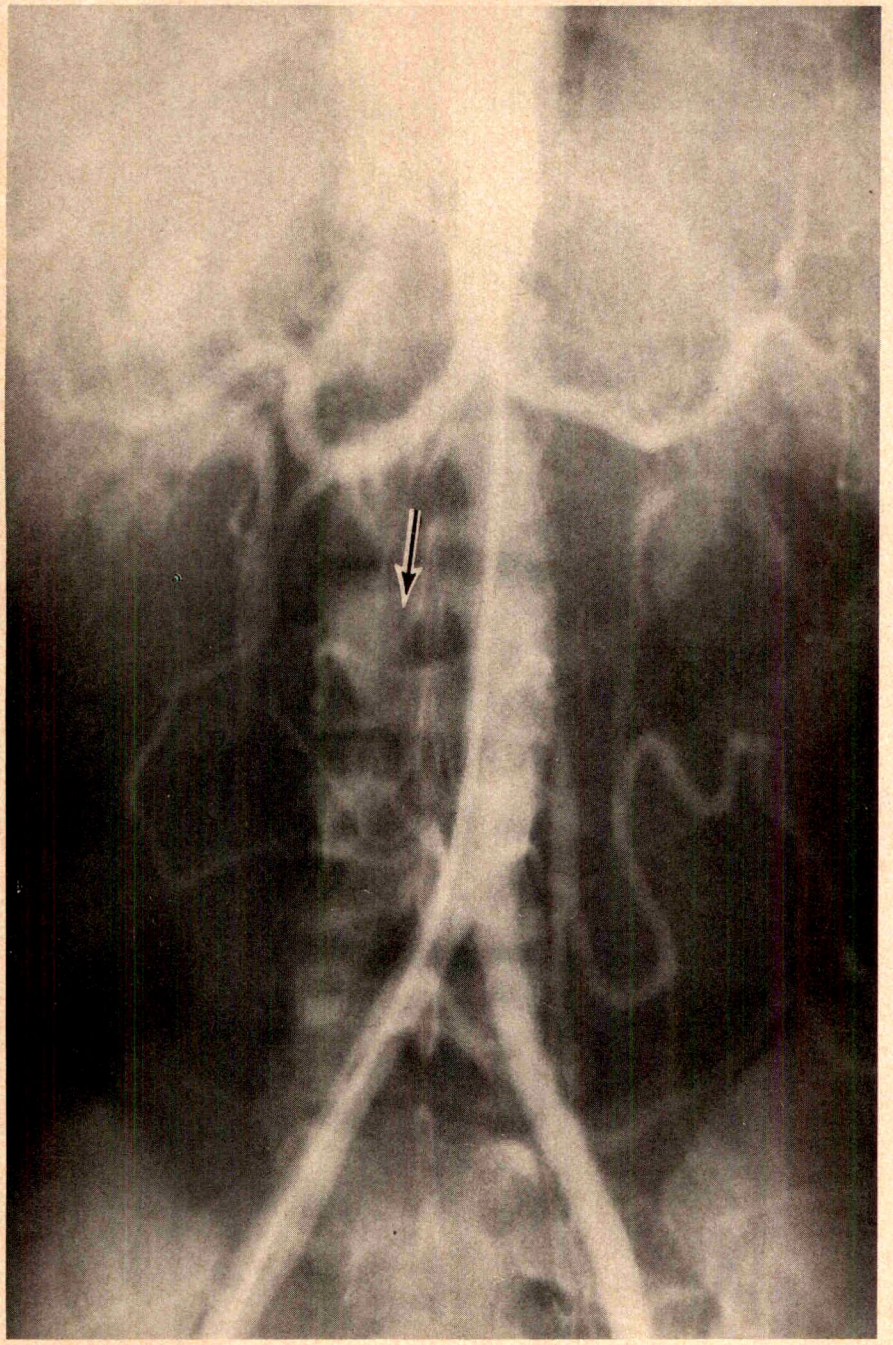


Fig 5.—Abdominal aortogram showing aortic wall irregularity. Renal arteries are not visualized. Superior mesenteric artery is partially occluded (arrow).

including extensive disease of the aortic arch and thoracic and abdominal aorta. The absence of systemic symptoms, and of cerebral or ocular involvement is not unusual; a recent report indicates that in the vast majority of patients, systemic manifestations are absent or not recognized.[17] In the diagnosis of aortitis syndrome, careful palpation of radial pulses, blood pressure measurements in arms and legs, and auscultatory search for murmurs are essential.[11]

Of approximately 50% of the cases present with arterial hypertension,[3,10] the majority were attributed to the involvement of renal arteries.[18] However, only 15% to 20% of the cases in large reported series had definite renal artery stenosis.[3,10] Isolated involvement of the carotid artery (with hypersecretion of renin due to stimulation of carotid sinus) and stenosis of the abdominal aorta have also been postulated as mechanisms.[19,20] In our patient, systolic hypertension was found during catheterization of the ascending aorta but was not clearly detected in peripheral vessels. It is likely that the hypertension was due mainly to decreased aortic compliance and increased stroke volume, both secondary to aortic arteritis and aortic insufficiency. Nevertheless, peripheral and renal vein renin levels were slightly elevated.

Aortic insufficiency, which was present in our patient, has been reported in only 6% of TD cases;[21] the incidence in the very young is probably even lower. It may be secondary to dilation of the aortic annulus and to abnormalities of the aortic leaflets. It should be noted that detection of the aortic root dilation was made by ultrasound; to our knowledge, there are not other reports of echocardiograms in TD. Serial echocardiograms may be of value in assessing dilated aorta, the severity of aortic insufficiency, and increased afterload, when systolic hypertension is present. Clinically, obstructed vessels may be suspected from symptoms of ischemia (such as reduced peripheral pulses and regional differences in blood pressure), but the true extent of the arterial involvement should be determined by arteriography.[22]

The usual findings in patients with TD and ischemic renal involvement secondary to renal artery stenosis or thrombosis have been renal atrophy, infarct, or diffuse fibrosis and hyalinization.[9] Unique features of our patient are initial asymptomatic hematuria and proteinuria. The second renal biopsy specimen demonstrated glomerular involvement that was not present in a renal biopsy specimen taken one year before. The cause of the focal and segmental mesangial glomerulonephritis is unclear. The immunoglobulin and complement deposits in the second biopsy specimen (though only 1+) and hypergammaglobulinemia with noticeably increased levels of IgG and IgA, suggest an immunologic mechanism either initiating or perpetuating the disease. Although the finding of antiaortic

antibodies in these patients has been controversial,[23,24] there is increasing evidence to indicate an autoimmune mechanism.[13] It is not yet clear whether circulating antiarterial antibodies are the direct cause of TD.

To our knowledge, an interval of less than one year between onset of glomerular involvement and clinically detected aortitis has not been previously documented in TD. A history of acute glomerulonephritis was found in six of 52 patients with arteritis syndrome but in those cases diagnosis was based only on clinical information and the episodes preceded TD by four years or more.[11] Streptococcal infection has been postulated as a trigger mechanism in the pathogenesis of TD.[23] We were unable to prove streptococcal infection by culture or serologic studies in our patient. Other possible causes, such as systemic lupus erythematosus or infective endocarditis were ruled out. Berger disease (IgA-IgG nephropathy) was not considered in our diagnosis since episodes of gross hematuria were not associated with intercurrent infections and serum IgG elevation is not usually described in this entity.

Finally, coincidental presentation of separate entities is a possibility. However, the glomerular and aortic involvement in this patient may be derived from common immunologic mechanisms. We would like to postulate that the glomerulonephritis developed as a result of trapping of aorta antibody complexes by the kidney. The worsening of the arteritis detected clinically at the level of the aortic root and aortic arch and the renal involvement detected in the second renal biopsy support this hypothesis. Evaluation of long-term response to immunosuppressive therapy might be helpful to clarify the mechanisms involved in the aortitis and glomerulonephritis of patients with TD.

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Abnormalities of In Vitro Lymphocyte Response to Mitogens in Diabetic Children During Acute Ketoacidosis

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• **Cell-mediated immunity was evaluated in 11 children with diabetes mellitus; six children were evaluated during ketoacidosis and five were evaluated with ketonuria in the absence of acidosis. Five of the six ketoacidotic children had at least one positive delayed-hypersensitivity skin test. Lymphocytes from two ketoacidotic patients were unresponsive to phytohemagglutinin and pokeweed mitogen, and lymphocytes from these two patients plus a third patient were unresponsive to concanavalin A. Lymphocytes from all six patients responded to these three mitogens after one week of therapy.**

In the five diabetic children without ketoacidosis, lymphocyte responses were normal to all three mitogens. Similarly, the addition of glucose to normal plasma did not alter the lymphocyte transformations of three healthy nondiabetic controls. These data suggest that cell-mediated immunity may be transiently defective in children with acute diabetic ketoacidosis.

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Depressed cell-mediated immunity is associated with an increased susceptibility to fungal and other unusual infections,[1] and patients with diabetes mellitus are more often afflicted with unusual infections than are nondiabetic patients.[2-4] Lymphocyte studies from a limited number of diabetic patients have shown both normal and depressed transformation responses,[5-8] but quantitatively normal B and T cell subpopulations.[5] Preliminary reports suggest that lymphocyte function in patients with diabetes mellitus may be related to the status of diabetic control.[5,9] Therefore, lymphocyte transformations (to phytohemagglutinin [PHA], pokeweed mitogen [PWM], concanavalin A [Con A], and specific antigens) and delayed-hypersensitivity skin tests were evaluated in patients with acute diabetic ketoacidosis to determine the duration and the extent of abnormalities in cell-mediated immunity.

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SUBJECTS AND METHODS

Patient Characteristics

Eleven patients, 10 to 17 years of age, with juvenile-onset diabetes were studied after informed consent was obtained. Ten of the patients had been insulin dependent for five years or longer but one patient's condition was initially diagnosed at the time of entry into this study when she came to us with acute ketoacidosis. Six patients, all female, had lymphocyte studies done more than once while in the hospital for treatment of ketoacidosis. The criteria for study included an initial urinalysis with 4+ amounts of glucose, large amounts of ketones, and a plasma pH of less than 7.3 (range, 6.8 to 7.18; mean, 7.06). The initial blood glucose levels ranged from 238 to 528 mg/dl (mean, 390 mg/dl). Episodes of ketoacidosis had begun five to 36 hours (mean, 16 hours) prior to hospitalization. Ketonuria cleared eight to 108 hours (mean, 44 hours) after admission. Skin tests were applied on the day of admission. Blood for lymphocyte studies on age- and sex-matched, healthy controls admitted for elective surgery was obtained and run simultaneously. Five other patients (three females and two males) had lymphocyte studies done once each during episodes of mild ketonuria (small to moderate amounts of ketones) without acidosis. The urine glucose content for these five patients ranged from 1+ to 4+ by dipstick and the blood glucose level ranged from 258

to 387 mg/dl (mean, 327 mg/dl). None of the diabetic patients had a history of unusual or frequent infections.

Skin Tests

Antigens used were PPD (5 tuberculin units/0.1 ml), *Candida albicans* (1:100 or 1:500 dilution), streptokinase-streptodornase (SK-SD) (diluted 1:5 or 1:50), histoplasmin, and Dermatophyton (diluted 1:30).

One tenth milliliter of each antigen was injected intradermally on the volar aspect of one forearm. Induration was measured at 48 and 72 hours and noted as positive if greater than 5 mm.

Lymphocyte Transformations

Fifteen milliliters of venous blood, anticoagulated with 500 units of preservative-free heparin sodium were centrifuged over Ficoll-Hypaque at 400 × g for 40 minutes. The lymphocytes were removed by pipette, washed with phosphate-buffer saline (pH of 7.4), resuspended in a mixture of tissue culture medium containing 20% autologous plasma and 100 units/ml penicillin G sodium and 100 μg/ml streptomycin sulfate, and counted. In some cultures, plasma from a healthy AB-positive donor was substituted. Triplicate lymphocyte cultures were established in microtiter plates. To each well was added 10^5 small lymphocytes (without correction for monocyte contamination) and one of the following: phytohemagglutinin (PHA), 6.25, 12.5, 25, 50, and 165 μg/ml; ConA, 10 μg/ml; PWM, 1:10 dilution; SK-SD, 12.5 units/ml; *C albicans*, 1:5 dilution; PPD and staphylococcus toxoid, 10,000 units/ml. Antigens with chemical preservatives were dialyzed extensively prior to use. Lymphocytes from all the patients and controls were also cultured without antigens to determine background transformations.

All the cultures were incubated at 37 °C in a 5% CO_2 humidified atmosphere. After 120 hours of incubation, 1 μCi of tritiated thymidine (specific activity, 20 Ci/mmole) was added to each well and incubation was continued for six hours. Cultures were then harvested onto glass-fiber filter paper with a multiple-sample precipitator. Filter papers were washed several times with 0.85% NaCl and air dried. Samples were then immersed in toluene scintillator and the radioactivity measured with a liquid scintillation counter. The arithmetic means of the triplicate samples were calculated and from these the background (unstimulated) values were subtracted. Counts were recorded as scintillation counts per minute (cpm). The data were statistically analyzed with the Wilcoxon Matched-Pair Rank-Sum Test,[10] which was deemed most appropriate for the small sample of patients studied.

RESULTS

Skin Tests

Five of the six patients (designated 1 to 5) in acute ketoacidosis responded to *Candida* and three of these five reacted to SK-SD as well. None responded to Dermatophyton, histoplasmin, or PPD. Only one was unresponsive to all five antigens but had normal lymphocyte transformations (patient 6).

Lymphocyte Transformations

Lymphocyte responses to PHA, ConA, and PWM were studied while the diabetic patients were in acute ketoacidosis at the time of admission, six to 12 hours after treatment was initiated, and after one week (Table 1). These lymphocytic responses were compared with results obtained with lymphocytes of diabetic patients with mild ketonuria, age- and sex-matched controls, and adult laboratory personnel. Lymphocytes of all the subjects studied responded maximally to PHA at doses of 25 to 165 μg/ml. Responses to 50 μg/ml of PHA were therefore chosen for intergroup comparisons of test values. Values less than 10,000 cpm were considered abnormal for each of the three mitogens since all age-matched and ten of the 12 laboratory controls exceeded this transformation value (Table 1). Responses to specific antigens (SK-SD, *C albicans*, PPD, and staphylococcus toxoid) were similar in diabetic patients and in both control populations. There were a large number of nonresponders among the controls, probably due to poorly standardized reagents. Consequently, these results are not reported here.

Mitogenic Responses

Lymphocyte transformation responses to PHA of diabetic patients in acute ketoacidosis on admission were significantly below those of laboratory controls ($P < .05$) (Table 1). Lymphocytes from two of the six diabetic patients in ketoacidosis were unresponsive to PHA, 50 μg/ml, on admission (patient 1, 362 cpm; patient 2, 1,469 cpm) (Table 2). These abnormal lymphocytic responses improved rapidly with treatment in patient 2 after eight hours (26,654 cpm). Patient 1 showed a normal transformation response in convalescence (47,026 cpm) but unfortunately her lymphocytes were not studied within six to 12 hours of admission. Lymphocyte transformation responses to ConA of diabetic patients in acute ketoacidosis on admission were significantly lower than those of the same patients in convalescence ($P < .025$). Lymphocytes from three of the six diabetic patients in acute ketoacidosis were unresponsive to ConA (patient 1, 174 cpm; patient 2, 3,862 cpm; patient 3, 9,583 cpm) but all had normal test values in convalescence (patient 1, 78,431 cpm; patient 2, 53,262 cpm; patient 3, 16,390 cpm). The condition of patient 3 was initially diagnosed as diabetic at the time of this admission. Lymphocytes from two of the six diabetic patients in acute ketoacidosis were unresponsive to PWM (patient 1, 5,758 cpm; patient 2, 277 cpm). Both reverted to normal test values in convalescence (patient 1, 74,454 cpm; patient 2, 27,515 cpm). Lymphocytes from diabetic patients with mild ketonuria responded normally to PWM, PHA, and ConA mitogens.

Effect of Therapy

The mean lymphocytic responses of diabetic patients in ketoacidosis increased greatly for each mitogen from the time of admission, to six to 12 hours later, and further during convalescence (Table 1). The lymphocyte transformation responses for diabetic patients in convalescence significantly exceeded the test values for age-matched controls with PWM ($P < .016$) and PHA ($P < .004$), and the responses exceeded the test values of the laboratory controls with ConA ($P < .05$) and with PWM ($P < .02$). When lymphocyte transformations of ketoacidotic patients were studied prior to any therapy (patients 1 through 3), their responses to PHA, ConA, or PWM were low (cpm, <10,000). In the other three, (patients 4 through 6), treatment had been started (intravenous [IV] hydration, IV sodium bicarbonate, and insulin) four to six hours before blood was

Table 1.—Lymphocyte Transformations in Diabetic Patients With Ketoacidosis and Mild Ketonuria

Mitogen Tested*	Patients With Ketoacidosis			Patients With Ketonuria, Without Acidosis	Control Subjects	
	On Admission	After 6-12 hr	Convalescent		Age-Matched	Laboratory
PHA, 50 μg/ml	4†/6 19,379‡	5/5 38,154	6/6 46,704	5/5 27,593‡ ± 15,829§	5/6 20,534 ± 10,911	12/12 50,361 ± 29,505
ConA	3/6 17,120	5/5 37,480	6/6 58,591	5/5 50,060 ± 16,736	6/6 37,622 ± 17,578	10/12 32,534 ± 15,788
PWM	4/6 30,179	4/5 46,138	6/6 60,414	5/5 43,355 ± 18,744	6/6 28,936 ± 9,419	11/12 38,320 ± 19,547

*PHA indicates phytohemagglutinin; ConA, concanavalin A; PWM, pokeweed mitogen.
†Indicates the number of responders (> 10,000 scintillation counts per minute) per group in counts per minute.
‡Indicates arithmetic means in counts per minute.
§Indicates SDs in counts per minute.

Table 2.—Lymphocyte Transformations of Individual Diabetic Patients in Acute Ketoacidosis and Convalescence

Patient	Mitogen Tested*						Initial Serum pH	Duration of Ketonemia During Treatment, hr
	PHA		ConA		PWM			
	Acute	Convalescence	Acute	Convalescence	Acute	Convalescence		
1	362	47,026	174	78,431	5,758	74,454	7.12	108
2	1,469	42,142	3,862	53,262	277	27,515	6.8	48
3	11,210	30,418	9,583	16,390	60,898	60,684	7.05	6
4	17,050	74,685	17,408	98,309	23,473	65,722	7.10	24
5	68,454	45,851	48,925	44,619	51,138	71,527	7.18	36
6	17,730	40,104	22,773	60,540	39,535	62,587	7.10	20

*PHA indicates phytohemagglutinin; ConA, concanavalin A; PWM, pokeweed mitogen.

drawn for lymphocyte studies. These latter patients were still in ketoacidosis but their lymphocytes showed higher test values than did those of the untreated patients. Their responses to one or all of the mitogens nonetheless increased during treatment.

Effect of Plasma

No consistent depression in lymphocyte transformations occurred when normal lymphocytes were cultured with plasma obtained from diabetic patients in acute ketoacidosis. Similarly, no consistent improvement greater than the normal error of the method was seen when lymphocytes from three diabetic patients (2, 5, and 6) in acute ketoacidosis were cultured with normal (homologous) plasma. Arithmetic mean responses with autologous and homologous plasma, respectively, were as follows: PHA, 29,217 and 40,473 cpm; ConA, 25,186 and 53,590 cpm; PWM, 30,316 and 34,017 cpm. Although a trend seems to be present, statistical significance is not. This is probably due primarily to the small sample size. When lymphocytes from three control donors were cultured with autologous plasma that was adjusted to varying glucose concentrations (300, 500, or 700 mg/dl), no changes were seen in transformation response to PHA, ConA, or PWM.

COMMENT

During diabetic ketoacidosis, a profound but transient depression in lymphocyte transformations to at least one mitogen occurred in three of the six patients tested. These impaired lymphocyte transformations reversed within hours after treatment was initiated, usually while the patient was still ketonemic. Lymphocyte transformations to all mitogens reverted to normal values within a week of the initial study in all patients. In fact, a slight rebound effect was seen whereby mitogenic values exceeded those of normal controls. It seems that in diabetic children, the ketonemic state must be metabolically uncompensated before abnormalities occur in lymphocyte transformations. Normal lymphocyte transformations were found in five patients who had mild ketonuria and hyperglycemia but no acidosis. Paradoxically, delayed-hypersensitivity skin testing was normal in five of the six patients in acute ketoacidosis. All patients with greatly reduced values for lymphocyte transformations had positive skin tests to one or more antigens, indicating an absence of true anergy. Similar dissociations between lymphocyte transformations and skin testing have been previously described during other illnesses.[11]

Our data concur with those of previous studies that showed that patients in good diabetic control have normal lymphocyte transformations while those in poor control have depressed responses.[5,9] These other authors suggested that the lymphocytic defect is a transient "metabolic abnormality" rather than a permanent immunologic derangement. Our data support this contention and further indicate the rapid reversibility of these defects. Causes for these transient abnormalities and their clin-

ical importance are unknown. Hyperglycemia should probably not be implicated since we found that varying glucose concentrations did not adversely effect transformations of lymphocytes from normal subjects. No circulating inhibitors of lymphocyte transformation were found in the plasma of diabetic children. However, acidosis, ketosis, and hyperlipidemia could act independently or in concert to alter lymphocyte function. A transient abnormality in the lymphocyte membrane[12,13] or in its internal metabolism could well be invoked.

Ketoacidosis exerts other deleterious effects on the immunologic system, including impairments of bactericidal capacity[14,15] and of the local exudative cellular response.[16] Fatal mucormycosis develops in diabetic rats in ketoacidosis when inoculated with this fungus, whereas normal rats become only locally infected.[17] Similarly in humans, most cases of mucormycosis have occurred in diabetic patients in ketoacidosis or in very poor diabetic control.[18,19]

In conclusion, these preliminary studies showed that transient in vitro defects in cell-mediated immunity occur during acute diabetic ketoacidosis.

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Mary Lou Magilavy assisted with the statistical analyses, Emil Reinhalter and Elizabeth Corwin provided laboratory assistance, and Paul Quie, MD, reviewed the manuscript.

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CORRECTION

Errors in Tables and Text.—In the article titled "Growth Hormone Deficiency, Brain Development, and Intelligence," published in the June JOURNAL (132:565-572, 1978), several errors occurred in the text and in Tables 1 and 2. In Table 1, column 4 (Inactive HGH) instead of column 3 should have an "X" under it for the Frankel and Laron entry. In Table 2, column 12 (Gonadotropins), the PE-10 entry under this column should have a paragraph symbol, not the section mark symbol. On p 566, right text column, fifth and sixth lines from the bottom should read "(based on Tables 2-5 and 2-6 . . .)" not 2 through 5 and 2 through 6. On p 567, left text column, third line from the bottom it should read "$\leq 8\ \mu g/100$ ml." And on p 567, middle text column, sixth line from the top, it should read "17-OHCS," and not "17-OHCS."

Ring Chromosome 13 in a Child With Minor Dysmorphic Features

Irregular Phenotypic Expression of Ring 13 Syndrome

Ram S. Verma, MSc, PhD; Harvey Dosik, MD; Imtiaz H. Chowdhry, MD; Ramesh C. Jhaveri, MD

• A patient with ring chromosome 13 had some physical stigmata that to our knowledge have not been reported in previous articles. These include alopecia, scattered pigmentation, trigonocephaly, and telecanthic fold. This case reemphasizes how mitotic instability can produce clinical features during the critical period of organogenesis.

(*Am J Dis Child* 132:1018-1021, 1978)

As a result of the recent advent of banding techniques, several investigators have been able to correlate phenotypic abnormalities with specific bands on chromosomes.[1,2] Based on the literature, some authors have suggested that patients with "ring" chromosomes would be phenotypically similar, and attempts have been made to associate special rings with definite malformation syndromes. A distinct syndrome caused by partial monosomy for the long arm of chromosome 13 is assumed to exist. However, several investigators reject the existence of definite ring syndromes and have strongly suggested that different patients with rings of a particular chromosome would display diverse clinical features.[3,4] We report a case of ring chromosome 13 (r13) and compare the physical characteristics of our patient with those of previously described patients with r13 syndromes. It appears that the r13 syndrome presents a variable phenotype that makes diagnosis on a clinical basis difficult. There are varying degrees of mitotic instability in patients with r13 syndrome, thus resulting in a population of cells with a variable genotype with subsequent variability of phenotypic expression.[5-10]

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Table 1.—Comparison of Clinical Features of Our Patient With 19 Previously Reported Cases

Clinical Features	Frequency of Symptoms	Features in Our Patient*
Low birth weight/small for gestational age	20/22	+
Arrhinencephaly	4/5	—
Microcephaly and mental retardation	22/22	+
Hypertelorism	18/19	—
Epicanthic fold	17/18	—
Broad prominent nasal bridge	16/17	+
Auricle (large, deformed, or low set)	16/19	—
High-arched palate	8/22	+
Protruding maxillary incisors	8/22	—
Micrognathia	11/22	—
Heart murmur	8/16	—
Hand and foot abnormality	10/22	—
Renal defect	2/22	—
Alopecia	NR†	+
Scattered pigmentation	NR	+
Trigonocephaly	NR	+
Telecanthic fold	NR	+

*+ indicates present; —, absent.
†NR indicates not reported.

REPORT OF A CASE

The patient was born Aug 17, 1974, the product of a 38-week gestation. The ages of her mother and father were 41 and 48 years, respectively. The patient is the last child of healthy parents. There was no consanguinity of either parents or grandparents. The mother had gestational diabetes for which no medication was prescribed. There was no history of unusual medication and the antenatal period was uneventful. All eight siblings are normal. At birth the patient weighed 2,160 g, and the head circumference was 31.5 cm. The Apgar score was 6 and 8 at one and five minutes, respectively. She was treated with phototherapy for neonatal hyperbilirubinemia. Her psychomotor development has been slow compared with other siblings. The patient was admitted to the Jewish Hospital and Medical Center of Brooklyn (NY) with a history of diarrhea and failure-to-thrive. At 2 years 8 months her head circumference was 43 cm, her height was 81 cm, and her weight was 10 kg. All physical values were below the third percentile. Positive physical findings included the following: microcephaly, trigonocephaly, telecanthus, a broad nasal bridge (a trait shared by the mother and siblings), a high-arched palate, a left preauricular sinus, a long philtrum, scattered alopecia (especially on the occiput), bilateral symmetrical depigmented spots on the arms and shoulders, mild talipes, pes planus, and bilateral clinodactyly. The following findings were not present: malformed or low-set ears, arrhinencephaly, epicanthus, microphthalmia, hypertelorism, prominent incisors, micrognathia, malformation of the tongue, or thumb, and cardiac or renal abnormalities. The patient had some physical characteristics that have not been reported in other cases of r13 syndrome (Table 1). Results of ophthalmologic and audiometric examinations were within normal limits. Findings of a neurological evaluation and bone age were compatible with 1½- to 2-year chronological age. Dermatoglyphic findings included an increase in arches (2/10) and radial loops (2/10), and a lower ridge count (56). Palmar patterns were unremarkable. The atd angle was normal. There were no abnormal crease patterns. The main line exits were normal and there were no high pattern intensities (Fig 1).



Fig 1.—Top left, Patient aged 3 years 3 months. Top right, Facial features. Bottom left, Side view. Bottom right, Back of head showing loss of hair.

RESULTS

Cytogenetic Findings

Chromosome preparations were made from short-term lymphocyte and skin fibroblast cultures. The following sequential banding tech-

Table 2.—Number of Metaphase Spreads Studied

Banding Technique*	Tissue	No. of Metaphases With Chromosome Counts: 46, XX, −13, +r13	47, XX, −13, + Two Rings	45, XX, −13
GTG	Peripheral blood	18	2	
Conventional	Peripheral blood	13		2
Conventional	Skin fibroblasts	18		2
QFQ and RFA	Peripheral blood	19	1	
CBG	Peripheral blood	24		1
Total		**92**	**3**	**5**

*GTG indicates G bands by trypsin using Giemsa stain; RFA, R bands by fluorescence using acridine orange stain; CBG, C bands by barium hydroxide using Giemsa stain.

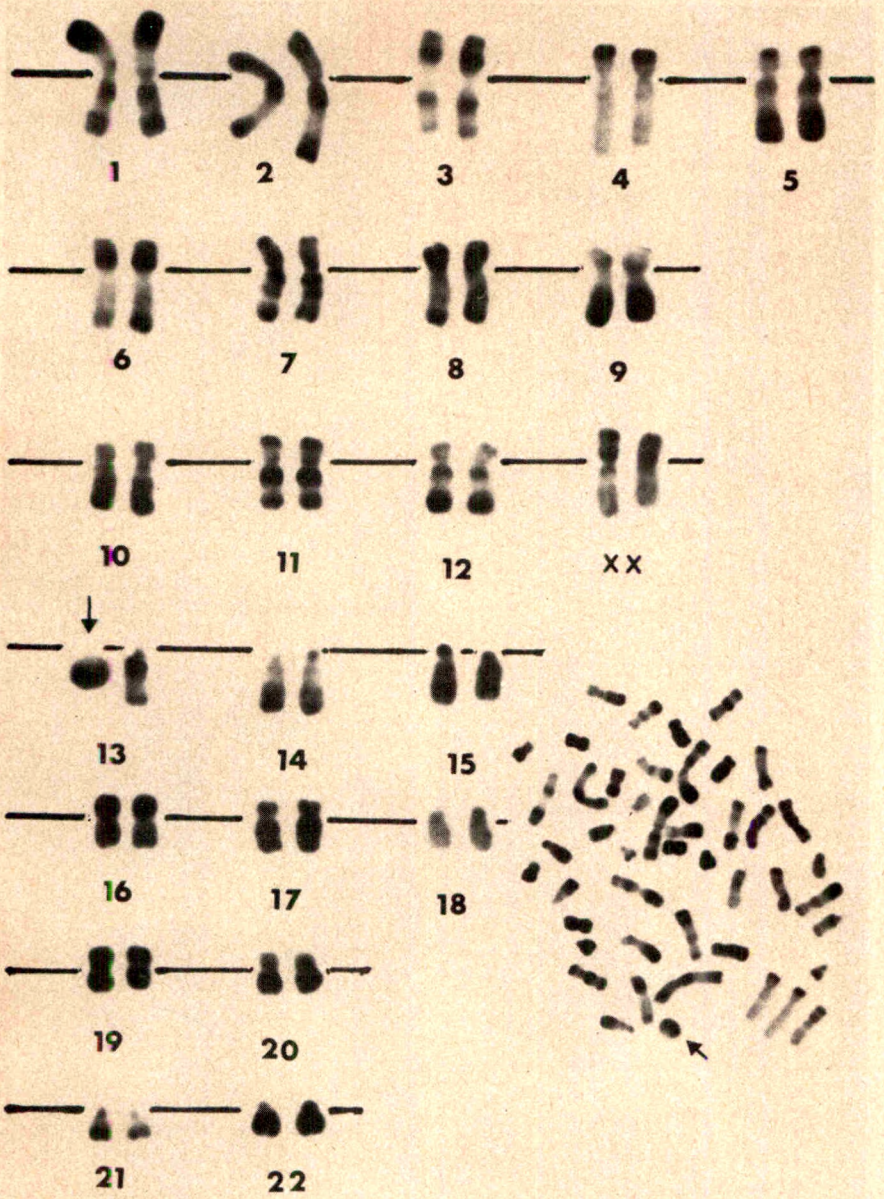


Fig 2.—Complete karyotype of patient showing r13 chromosome (R bands by fluorescence using acridine orange stain).

Fig 3.—Partial karyotype of D-group chromosomes (see text for explanation).

BANDING TECH.	CELL NUMBER 1	2	3
RFA			
QFQ			
GTG			

niques were used: Q bands by fluorescence using quinacrine hydrochloride (QFQ), R bands by fluorescence using acridine orange stain (RFA), G bands by trypsin using Giemsa stain (GTG), and C bands by barium hydroxide using Giemsa stain (CBG).[11-16] One hundred metaphases from the patient and 20 metaphases from each parent were examined. The QFQ-banded chromosomes were photographed using a photomicroscope. The CBG and GTG-banded chromosomes were photographed on high-contrast copy film; RFA-banded chromosomes were photographed on color film.

The distribution of chromosome counts in 100 metaphases is given in Table 2. A ring chromosome replaced chromosome 13 (Fig 2 and 3). The ring was proportionally small with an average diameter of a G-group chromosome and proved to be rather stable during mitosis (92% cells). Three metaphase spreads showed two rings, five had no rings, and two had double-sized rings (Fig 4). Through multiple-banding techniques, it was determined that the long arm was broken at region 3, band 4; and the short arm was broken at region 1, band 1 (ie, 46, XX, r13 [p11→q34]). Results of cytogenetic studies in both parents were normal.

COMMENT

The patient came to the hospital with gastroenteritis and was investigated for failure-to-thrive. Cytogenetic studies showed that she had a r13. A number of investigators have indicated that ring 13 exists as a clinical entity or entities.[5,6,9,17,18] Niebuhr and Ottosen[9] suggested three possible distinct clinical syndromes involving r13. These were based on the variable loss of genetic material from the long arm of chromosome 13 during the formation of the ring. In detecting these syndromes, partial deletion of the long arm of chromosome 13 was equated with a ring in which similar material was lost. Thus, three groups were identified: Group 1 involved the loss of segments 13q34 and 13q33 and was characterized by severe mental retardation, microcephaly with true hypertelorism, salient frontal bossing erasing the nose bridge, forward-

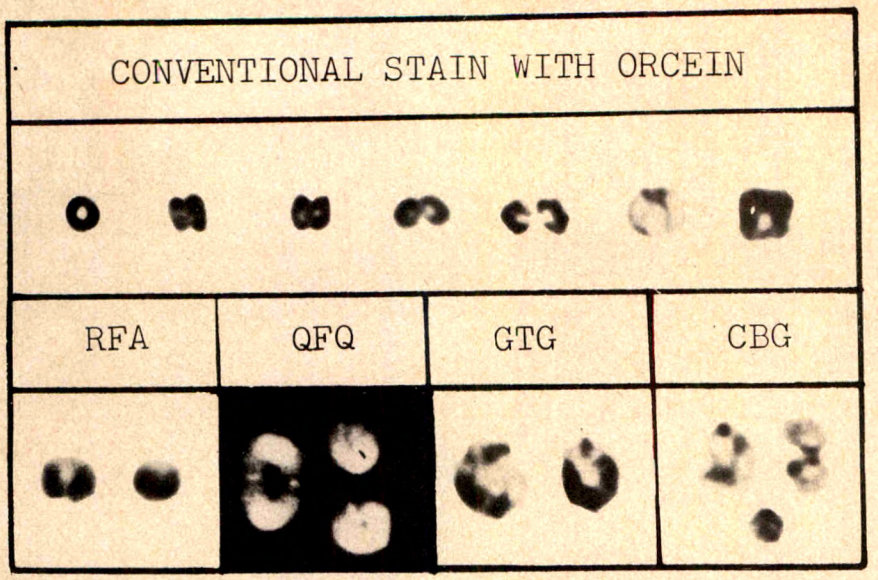


Fig 4.—Heteromorphism of ring chromosome showing one and two centromeres in ring by several banding techniques.

slanting maxillary incisors, and large ears with deep sulci helici. Group 2 was characterized by hypoplastic or absent thumbs and involved the additional loss of the segment 13q32 and part of 13q31. Group 3 involved an interstitial deletion of 13q21 and was found in patients with retinoblastoma. Others have questioned the existence of a r13 syndrome.[3,4,19]

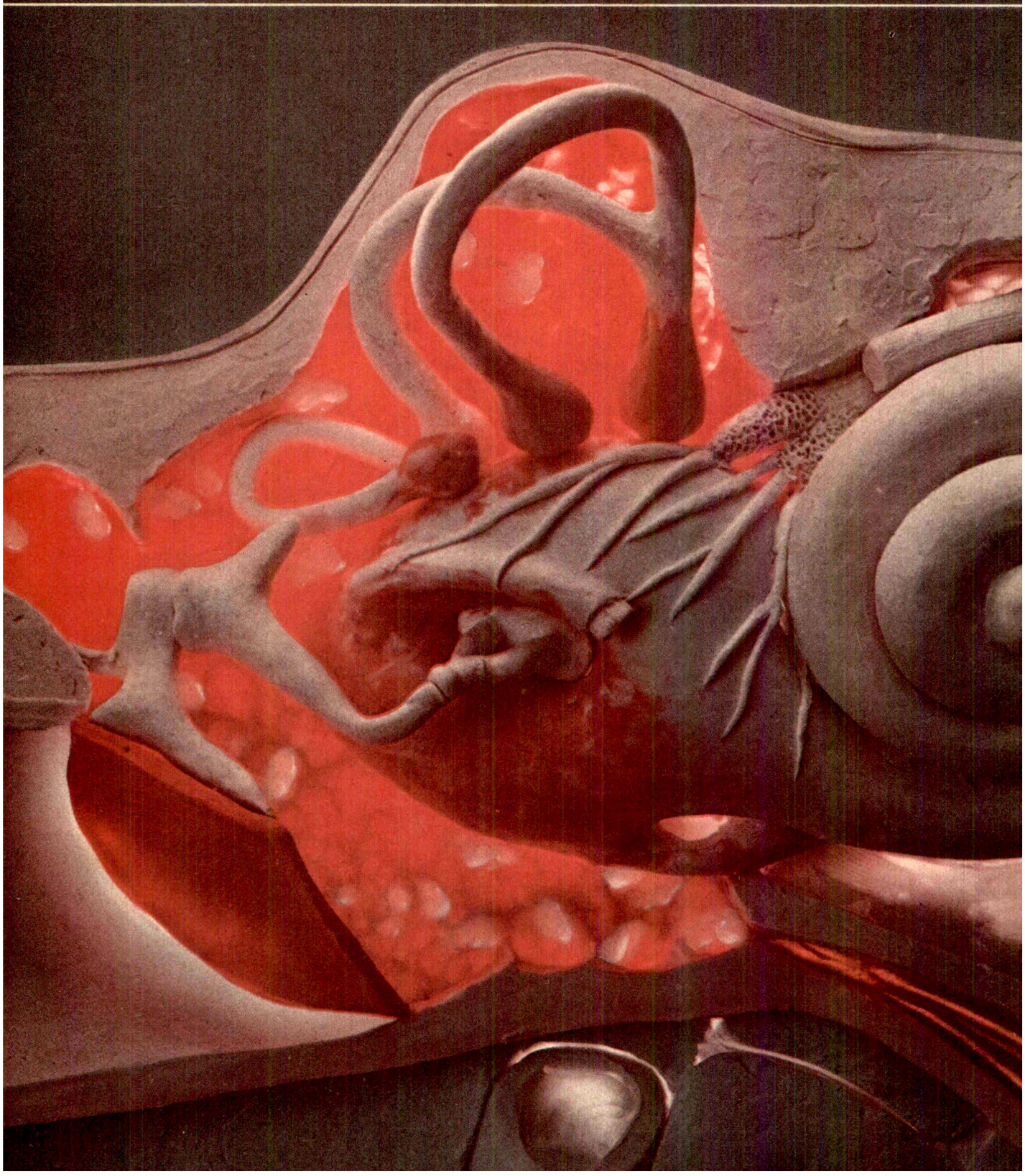
In our patient's case the short arm was broken at 13p11 with concomitant loss of bands 13p12 and 13p13, whereas the long arm was broken at 13q34 with a minimum loss and preservation of bands 13q31, 32, and 33. Deletion of the short arm of human acrocentric chromosomes does not have clinical consequences.[20] The clinically relevant segments in the case of r13 are located on the long arm.[21] Nevertheless, we were unable to explain the clinical features in our patient on the basis of the loss of specific bands during the formation of the ring. Mitotic instability, producing monosomy (5% of all cells) and partial double trisomy (3% of all cells), was also observed in this case (Table 2), which could explain the abnormalities. Hoo et al[7] described a patient with r13 in which the break points were similar to those in our patient. Clinical features included low birth weight, psychomotor retardation, a high-arched palate, bilateral epicanthic folds, a broad nasal bridge, relatively large ears with prominent anthelices, and deep sulci and micrognathia. The clinical features in their patient[7] were very similar to group 1 as described by Niebuhr and Ottosen[9] when 13q33 and q34 were missing. Recently, Noel et al[19] presented a map of chromosome 13 based on partial deletion and trisomies, and they correlated the clinical features in ring 13 with partial monosomy and trisomy. Our case reemphasizes the importance of mitotic instability in the production of clinical features,[1] and it raises serious questions that the existence of a r13 syndrome can be proved solely on the basis of the break points involved in the formation of the ring.

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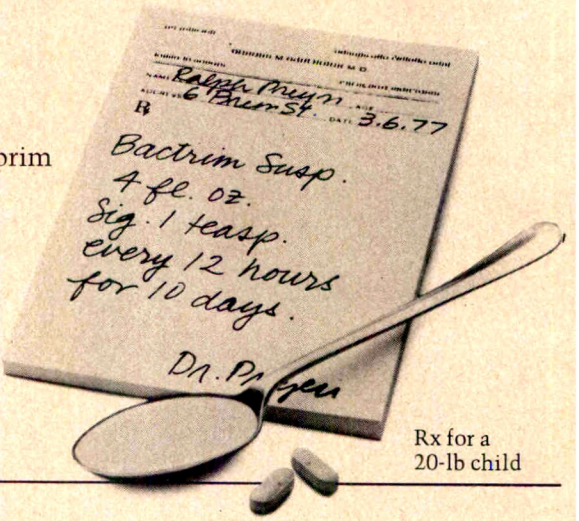
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For acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over other antimicrobials. Limited clinical information presently available on effectiveness of treatment of otitis media with Bactrim when infection is due to ampicillin-resistant *Haemophilus influenzae*. To date, there are limited data on the safety of repeated use of Bactrim in children under two years of age. Bactrim is not indicated for prophylactic or prolonged administration in otitis media at any age.

Also for the treatment of documented *Pneumocystis carinii* pneumonitis. To date, this drug has been tested only in patients 9 months to 16 years of age who were immunosuppressed by cancer therapy.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; pregnancy; nursing mothers; infants less than two months of age.

Warnings: BACTRIM SHOULD NOT BE USED TO TREAT STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A β-hemolytic streptococcal tonsillopharyngitis have higher incidence of bacteriologic failure when treated with Bactrim than do those treated with penicillin. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for infants less than two months of age.

URINARY TRACT INFECTIONS IN ADULTS AND CHILDREN AND ACUTE OTITIS MEDIA IN CHILDREN:

Adults: Usual adult dosage for urinary tract infections—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days.

Children: Recommended dosage for children with urinary tract infections or acute otitis media—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. A guide follows:

Children two months of age or older:

Weight		Dose—every 12 hours	
lbs	kgs	Teaspoonfuls	Tablets
20	9	1 teasp. (5 ml)	½ tablet
40	18	2 teasp. (10 ml)	1 tablet
60	27	3 teasp. (15 ml)	1½ tablets
80	36	4 teasp. (20 ml)	2 tablets or 1 DS tablet

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	½ the usual regimen
Below 15	Use not recommended

PNEUMOCYSTIS CARINII PNEUMONITIS: Recommended dosage: 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.

Supplied: *Double Strength (DS) tablets,* each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100; Tel-E-Dose® packages of 100; Prescription Paks of 20. *Tablets,* each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40, available singly and in trays of 10. *Oral suspension,* containing in each teaspoonful (5 ml) the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole, fruit-licorice flavored—bottles of 16 oz (1 pint).

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Resident Seminar

Pediatric Clinical Pharmacology

A Practical Review

Gail Udkow, MD

• Significant differences exist between children and adults in their handling of a large number of therapeutic agents. The relative immaturity of the pediatric patient and the continuous state of development of body and organ functions influence both drug effects and drug disposition. Daily dosage requirements vary with age. For many drugs, children require and tolerate much more of a drug, relative to their size, for the same effect. Newborns may need more or less of a drug for a comparable effect.

A conceptual framework is provided to aid in understanding the individuality of the pediatric patient's drug disposition processes based on differences in physiologic functions affecting drug absorption, distribution, metabolism, and excretion. Additional data are needed on drug disposition in children of all ages to maximize therapeutic drug usage with avoidance of toxicity.

(*Am J Dis Child* 132:1025-1032, 1978)

It is well recognized that children cannot be viewed as "little adults" with respect to either drug effects or drug disposition. Pediatric therapeutics and toxicology deal with an immature organism in a continuous state of development of body and organ functions. Drug effects on developmental processes that may be ongoing in the pediatric patient must also be considered.

The "drug disasters" of the 1950s and 1960s dramatically emphasized the individuality of the pediatric patient's response to drugs. When accepted doses of chloramphenicol were given to newborn infants with suspected or confirmed sepsis, unexpected deaths resulted from the "gray-baby syndrome." We now know that newborn infants, especially premature ones, cannot appropriately metabolize or excrete this drug because of hepatic and renal immaturity, and that the deaths probably resulted from inadvertent overdosage with resultant vascular toxicity.[1] Sulfisoxazole therapy for sepsis caused kernicterus even with low levels of serum bilirubin because of the drug's previously unsuspected interference with normal binding of bilirubin to albumin.[2] The thalidomide disaster brought attention to the possibility of inducing congenital malformations with a drug considered to be nontoxic to the adult.[3] More recently, diethylstilbesterol taken by pregnant women to prevent spontaneous abortion has resulted in vaginal adenocarcinoma[4] and structural urogenital anomalies in female offspring.

The Kefauver-Harris amendments of 1962 were passed in response to the preceding therapeutic misadventures, and required stringent Food and Drug Administration regulation of all testing of drugs on humans prior to marketing. Before 1962, the FDA evaluated the data on animals and humans only at the time the manufacturer sought governmental approval to market the drug, and the legal focus was on evidence of safety rather than efficacy.

Although this legislation and the consequent regulations were intended to protect children, they have not been totally beneficial to the pediatric patient. The FDA regulations require that a drug labeled for use in children must be investigated in children for its efficacy and safety. Relatively few data have been generated in children for drugs marketed since 1962, in large part because the complex medicolegal issues of experimentation in children[5] have not been settled in either the lay or professional spheres.

Without such data, the FDA will not approve labeling of a drug for use in the pediatric patient. Our patients are, therefore, "therapeutic orphans,"[6] restricted at least in theory from

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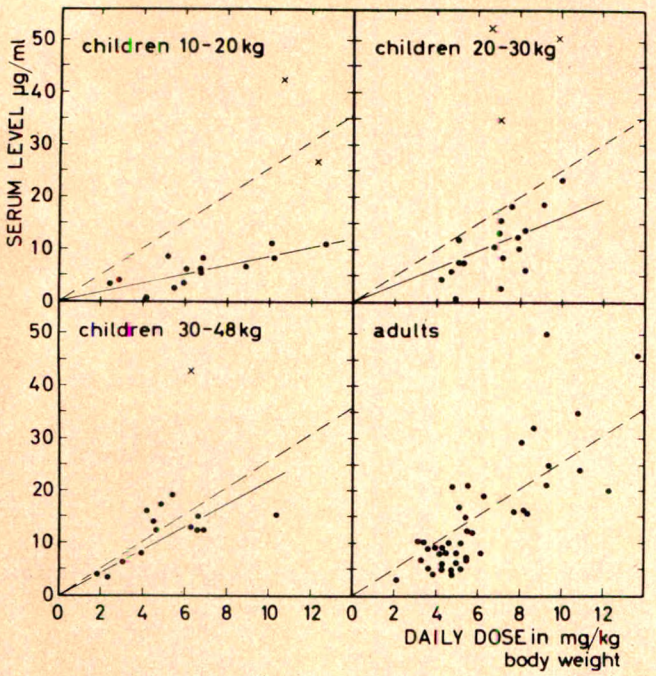


Fig 1.—Serum concentration of phenytoin as function of daily dose (milligrams per kilogram of body weight) in children and adults. Solid lines indicate data for children; broken lines, for adults. X was not included in regression analysis by original authors. Resultant serum concentrations were statistically significantly lower in children weighing less than 30 kg as compared to adults (from Svensmark and Buchthal[7]).

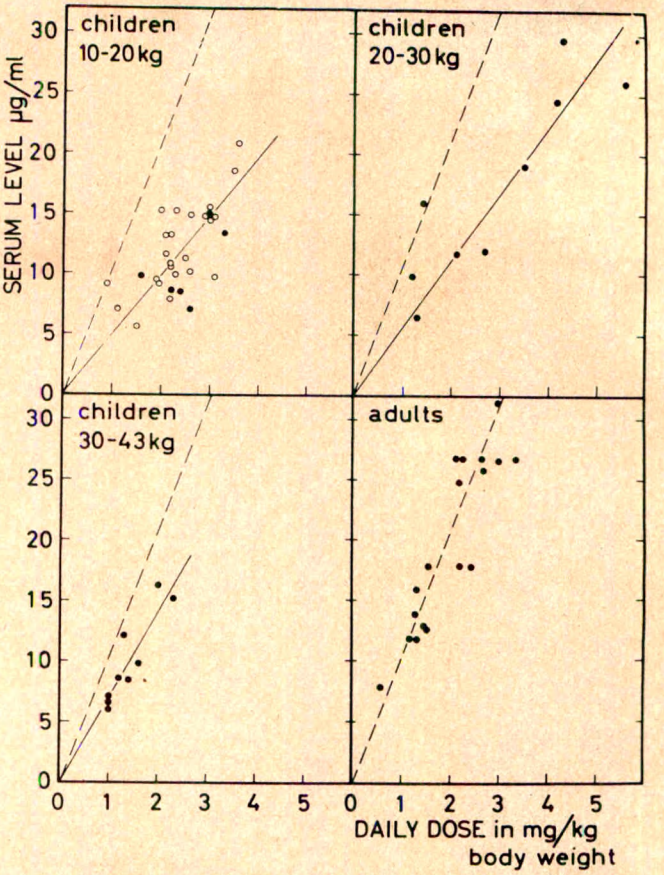


Fig 2.—Serum concentration of phenobarbital as function of daily dose (milligrams per kilogram of body weight) in children and adults. Solid circles indicate inpatients; open circles, outpatients. Solid lines indicate data for children; broken lines, for adults. Resultant serum concentrations were statistically significantly lower in children weighing less than 30 kg as compared to adults (from Svensmark and Buchthal[7]).

receiving drugs that have not been approved for use in the pediatric patient. The FDA requires manufacturers to include prohibitive clauses for a product's use, clearly stating that the drug "should not be used in children because data as to its efficacy and safety are lacking in this age group." As a result, we may be withholding excellent therapeutic agents or using toxic drugs or insufficient or toxic doses in our patients.

There is no simple valid means of extrapolating to children the dosage guidelines determined in adults. Dosage schedules based on body weight (milligrams per kilogram) may be insufficient in attempting to achieve a given serum concentration, as seen in Fig 1 and 2.[7] Surface area basis of dosage (milligram per square meter) may be more valid because this measurement correlates with some of the physiologic functions important in determining differences in pharmacokinetics in patients of different ages. However, this method is still not adequate.

Children require and tolerate greater daily doses of many drugs to achieve the same serum concentration or effect as adults. Newborns and infants may require more or less of a drug for a comparable effect. The goal, needless to say, is to achieve the desired therapeutic effect without toxicity, not to achieve an arbitrary drug concentration in blood or other body fluid. Incorrect drug dosages may interfere with this goal.

Despite the knowledge that drugs ingested by pregnant women may have untoward effects on the developing fetus or be handled differently by the newborn, worrisome prescribing patterns continue. A recent prospective study of a middle- to upper-class population of gravid women found a mean intake of 9.6 (range, 1 to 37) drug preparations during pregnancy, with a mean of 6.4 prescribed by the physician.[8]

The continuing use of tetracyclines in children also indicates inadequate application of the knowledge of the differential effects of agents on the developing organism. The Committee on Drugs of the American Academy of Pediatrics found no absolute indication for the use of tetracyclines in children less than 8 years of age,[9] reflecting in part the interference of these drugs with calcium metabolism and the risk of permanent enamel hypoplasia and staining.[10 (p1189)] Yet a recent review of tetracycline prescribing in a rural population found that 7% of children in this age group had received at least one tetracycline

prescription, more from surgeons and internists than from pediatricians.[11]

It is therefore obvious that major gaps exist in the application of the knowledge of the individuality of the pediatric patient's response to drugs. It is the purpose of this article to review the basic pharmacokinetic functions (absorption, distribution, metabolism, and excretion) as they may affect drug disposition in the newborn and older child. Several recent reviews have summarized the available data on specific drugs,[12-14] and these data will not be discussed here.

ABSORPTION

The rate at which a drug enters the bloodstream depends on the route by which it is given, and on the physicochemical properties of the drug that determine its passage across all membranes: molecular weight, lipid solubility, and degree of ionization.

For absorption from peripheral sites (intramuscular, subcutaneous), tissue perfusion is important. The vasomotor instability of the newborn may interfere with a drug's absorption from muscle or subcutaneous tissue. As in a patient of any age, shock with impaired peripheral circulation will result in decreased absorption, and a depot of drug will remain to be absorbed when blood flow stabilizes.

After oral dosing, most drug absorption takes place in the small intestine, which provides a very large surface area and a wide pH range (4 to 8) that favors the absorption of the nonionized absorbable form of most drugs.

Newborns have relative gastrointestinal dysfunction that may alter the speed and efficiency of drug absorption. The acidity of the gastric juices is not developed until 24 to 48 hours after birth. There may be a delay in maturation of intestinal enzyme systems necessary to alter the form of a drug before absorption can occur. In addition, intestinal motility may be markedly decreased, especially if the newborn suffers from cardiorespiratory or gastrointestinal disease that precludes oral feedings. Any of these alterations may influence dosage requirements and ultimate drug effects.

Beyond the newborn period, there are no functional differences between the healthy child and adult that should alter drug absorption from the gastrointestinal tract.

DISTRIBUTION

The apparent volume of distribution (AVD) is a useful mathematical expression, calculated by dividing the total amount of drug in the body by the theoretical plasma concentration that would exist, after instant equilibration, at time zero, following an intravenous bolus injection (Fig 3).[10 (pp20-21)]

$$\text{AVD (liters)} = \frac{\text{total drug in body (mg)}}{\text{plasma concentration (mg/liter)}}$$

This concept is important in drug dosing, that is, in calculating a "loading dose" necessary to achieve, without delay, a certain plasma drug concentration. The AVD describes

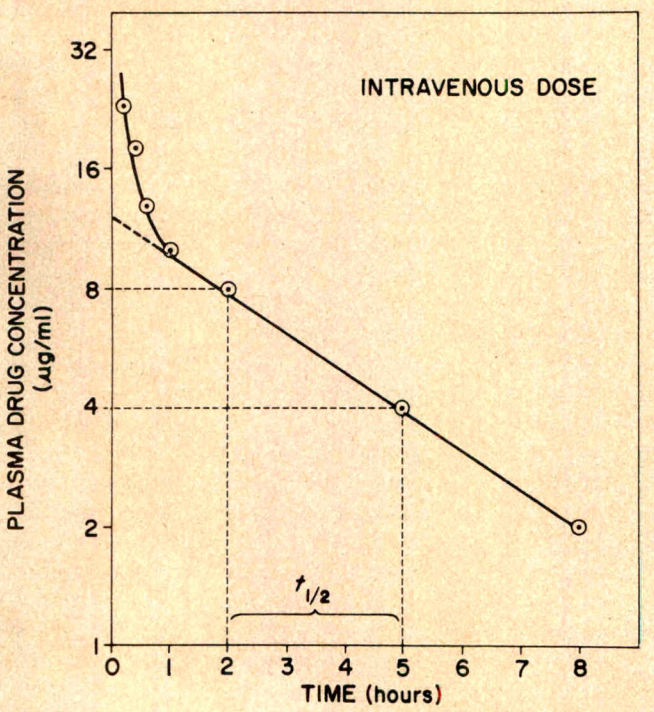


Fig 3.—Fundamental pharmacokinetic relationships for single dose of drug. A drug (500 mg) is administered intravenously and plasma samples are obtained for determination of drug concentration. Concentration falls rapidly initially, as distribution occurs. First-order elimination kinetics follow. Extrapolation of this line indicates hypothetical plasma concentration of 12 µg/ml at zero-time. The AVD = 500/12 = 41.7 liters. Half-time of drug elimination is estimated to be three hours (from Goodman and Gilman[10]).

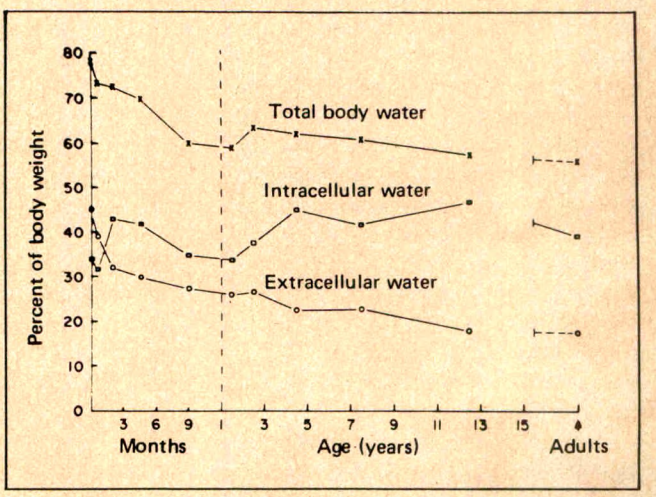


Fig 4.—Developmental changes in total body water, intracellular, and extracellular water in infants and children. Changes are expressed as percentages of body weight (from Rane and Wilson[12]).

that volume that must be filled with the drug before the desired plasma concentration can be achieved. If a drug is highly concentrated in tissues, the AVD can be much greater than the total body water, since the tissue sites would have to be saturated initially. The AVD is also useful in comparing different age groups or disease states in which intrinsic patient variables alter the distribution of the drug and therefore affect drug dosing.

There are only limited data available on distribution volumes in the pediatric patient, especially the newborn infant. For several drugs that have been studied, the AVD is relatively greater (*l*/kg of body weight) in the newborn period and throughout childhood as compared to the adult.[14] This may contribute to the increased dosage required for a desired effect or serum concentration.

There are several physiological alterations in children of different ages that may affect the volume of distribution. After entry into the bloodstream, drugs are delivered to the body tissues, eventually to interact with their receptors. The blood flow, mass, and fat content of a tissue will determine how much of the drug, carried in the bloodstream, will reach the tissue and be taken up by it. There is a continuous change in body weight and relative body composition throughout childhood. The relative body lipid content is lower in the newborn, especially the premature, but the central nervous system constitutes a greater percentage of the lipid mass in infancy. In addition, the blood-brain barrier of the newborn may be "leaky" and allow increased passage of some drugs across it. The relative mass of subcutaneous tissue increases to its greatest value at 9 months of age, decreases until 6 years of age, then begins to rise again as adolescence approaches. These changes will affect the distribution of lipid soluble drugs.

A variable believed to be important for drug distribution and in determining the higher dosage requirements in children is the change in the relative volumes of the body water compartments with age (Fig 4).[12] In addition to any tissue binding that may occur, drugs eventually distribute in the extracellular or total body water, so that the volumes of water available are important in determining the ultimate drug concentration achieved with a certain dose. Total body water (TBW) as a percentage of total body weight is much greater in the newborn—85% in the premature infant, 75% in the full-term infant—decreasing to 59% in the 1-year-old and to 55% in the adult. Similarly, extracellular water (ECW) as a percentage of total body weight decreases from 40% in the infant to 28% in the 1-year-old and to 20% in the adult. The most abrupt decrease in both TBW and ECW values occurs during the first year of life.

Drug binding to serum proteins, especially albumin, may be altered in the newborn period. It must be remembered that only free, unbound drug is available to migrate into body tissues and interact with receptors; drug bound to serum proteins is inactive and held in reserve. For drugs that are highly bound, a seemingly small change in the percent bound can significantly alter the amount that is free. For example, decreasing the percent bound from 95% to 90%, while decreasing bound drug by only 5%, will double the amount of free drug available.

There are both quantitative and qualitative differences in newborn albumin drug binding. Newborns, especially prematures, may have decreased concentrations of serum albumin, with "normal" values ranging from 2.5 to 5.0 g/dl. Newborn albumin also exhibits decreased binding affinity for certain drugs, with resultant increases in the free fraction. The presence of hyperbilirubinemia further increases the free fraction of the drugs studied, presumably by bilirubin displacement of the drug from its albumin binding site.[15-17]

The relationship between the degree of drug protein binding, changes that occur in the amount of free drug, and the resultant serum concentration is not a straightforward one. Increased amounts of free drug will increase availability to receptors, but also to some metabolic and excretory functions. In addition, some hepatic metabolic and renal tubular functions can eliminate both bound and free drug. The AVD of the drug may be altered without a change in the overall drug elimination. One therefore cannot readily predict the resultant net effect on a particular drug's pharmacokinetics.

METABOLISM

Metabolism and excretion together constitute the body's mechanisms for eliminating drugs. There are marked variations in rates of elimination in infants and children compared to adults.

The liver is quantitatively the most important organ for drug metabolism in all age groups. Drug biotransformation into inactive (or, less frequently, active) metabolites can be achieved through a variety of pathways: microsomal or nonmicrosomal oxidation, reduction, hydrolysis, and conjugation.

There is a change in the relative hepatic size with increasing age. The fetal liver is 4% of the total body weight; the adult liver is 2%. That is, there is a 50% decrease in the relative liver size, on a gram-per-kilogram body weight basis, from birth to adulthood. This provides the child with a markedly increased relative hepatic surface area available for drug metabolism and is important in determining the overall rate of elimination for those drugs that undergo hepatic metabolism.

The second important variable for drug metabolism is the quantitative change in the hepatic drug-metabolizing enzyme systems with increasing postnatal age. Immature animals in general have decreased enzymatic capabilities for those systems that have been studied. Application of animal data in this area is difficult, since there is marked variability between species and systems under study in terms of their degree of immaturity at birth and the time course of development to adult levels of activity.[18] In general, analysis of the human newborn's capacity to metabolize specific agents in common therapeutic use is still lacking.

In the newborn period, the balance

Physiologic Alterations That May Contribute to Variations in Pharmacokinetics in Children as Compared to Adults		
	Newborns	**Older Children**
Absorption	Subcutaneous, intramuscular vasomotor instability	. . .
	Oral ↓ Intestinal motility ↓ Gastric acidity Delayed intestinal enzyme development	. . .
Distribution	Relative organ mass, fat content, blood flow	Relative organ mass, fat content, blood flow
	"Leaky" blood-brain barrier	. . .
	Alteration in body water compartments	Alteration in body water compartments
	↓ Serum albumin	. . .
	↓ Albumin drug binding	. . .
Metabolism	Enzyme immaturity	. . .
	↑ Relative hepatic size	↑ Relative hepatic size
Excretion	↓ Glomerular filtration rate	. . .
	↓ Tubular function	. . .

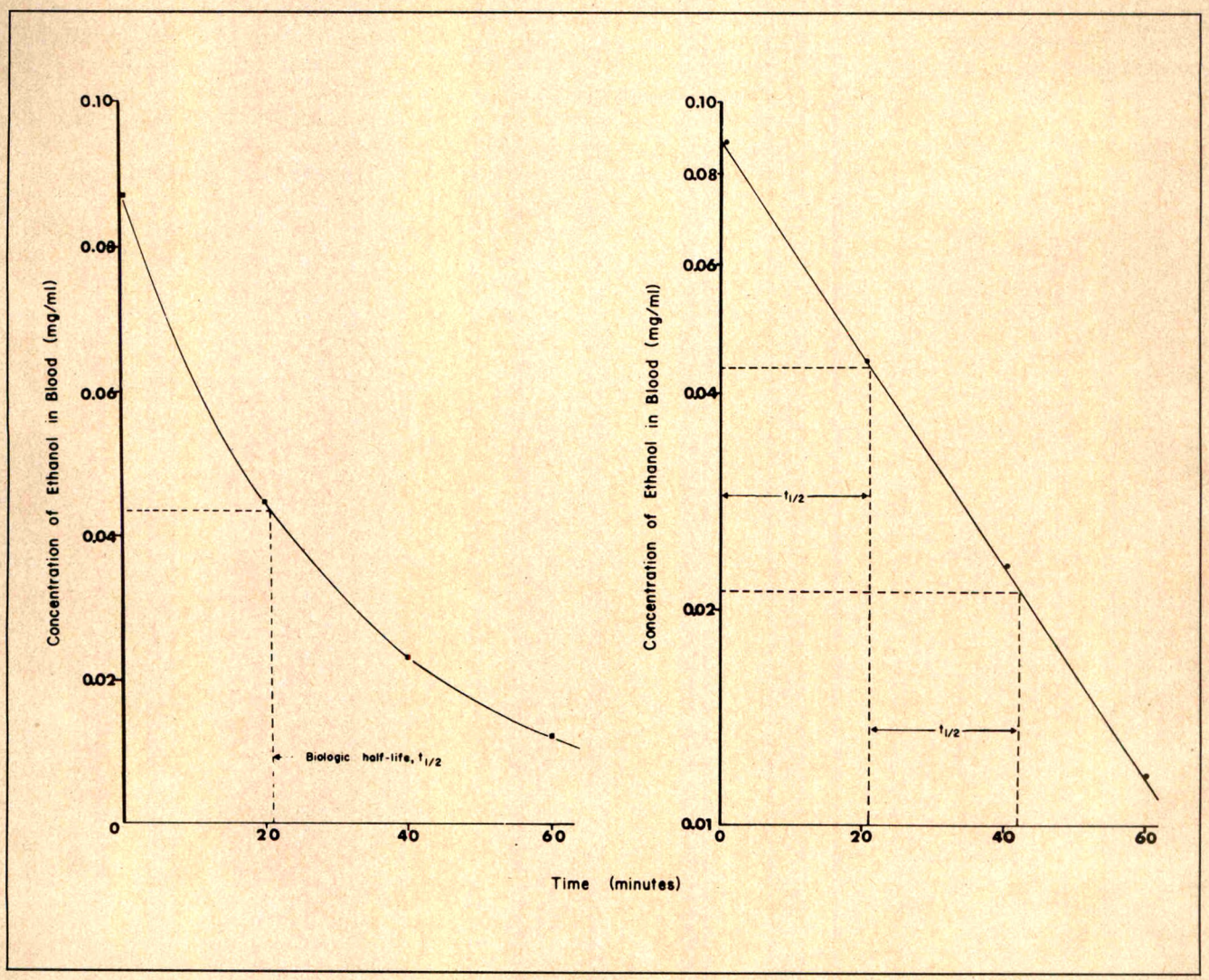


Fig 5.—First-order rate of elimination. Decline of ethanol content in blood following intravenous administration of a small dose. Left, Ordinate is concentration in blood on an *arithmetic* scale; right, on a *logarithmic* scale. Half-elimination time ($t_{1/2}$) is about 20 minutes (from Marshall and Fritz[33]).

of the increased hepatic surface area available for drug metabolism and the enzyme immaturity will determine the net ability of the patient to eliminate the drug in question. Most agents eliminated via this route have decreased rates of elimination in premature and fullterm newborns,[13,14,19-21] indicating an overall decreased hepatic metabolic capability. Where it has been attempted, correlation cannot be made between rates of elimination and any measurement of age: postnatal, postconceptual, gestational.[19-21] Thus, the degree of impairment of hepatic metabolism of an agent cannot be predicted without specific study in newborn children.

Newborns do not have decreased drug metabolizing capacity for all drugs. This especially pertains if transplacental exposure to a drug has occurred, for example, in chronic anticonvulsant therapy for the mother.[13,22]

In late infancy and childhood, many drugs are eliminated via hepatic metabolism at greater rates than in adults. Wide interindividual variations in rate of elimination occur in patients of all ages. Phenobarbital, phenytoin, carbamazepine, ethosuximide, propoxyphene, and theophylline, among others, have been studied in some detail in older children.[12,14,23-25] The increased elimination rates are assumed to reflect the increased relative hepatic size available for drug metabolism.

EXCRETION

Excretion is the ultimate route for drug elimination from the body, either as unchanged drug or as metabolites produced by the liver or other tissues. Excretion may occur through bile, feces, urine, or lungs, with the kidney the primary drug excretory organ.

As with the liver, there are developmental changes that occur in the renal drug-eliminating processes. In the newborn, the glomerular filtration rate (GFR) is decreased to 30% to 50% of the adult values, presumably as a result of increased renal vascular resistance with decreased renal blood flow, only 20% to 40% that of the adult. Tubular secretory and reabsorbing capacity is also impaired.

Many drugs depend primarily on renal excretion for elimination from the body, most importantly most antibiotics. Decreased renal function can greatly increase the time of a drug's sojourn in the body, and dosage adjustments must be made to avoid toxic drug serum concentrations and drug accumulation. However, not all drugs eliminated unchanged via the kidneys in the adult may follow this pattern. Colistin, for example, is excreted by glomerular filtration in the adult. Its elimination rate does not vary throughout the neonatal period, however, suggesting that it is being eliminated by the newborn via an alternate mechanism.[26]

Dosage schedules appropriate to the newborn's impaired renal excretory capability have been enumerated for

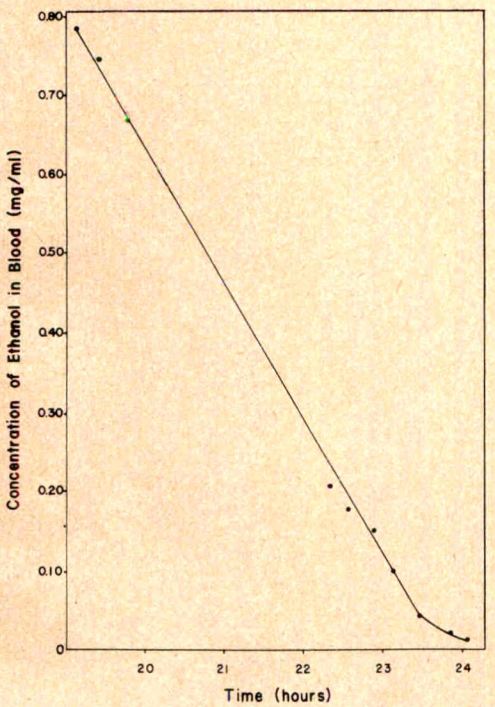


Fig 6.—Zero-order rate of elimination. Decline of ethanol content in blood following intravenous administration of a *large* dose. Ordinate is concentration in blood on an *arithmetic* scale. Change from zero-order to first-order kinetics occurs at low serum concentrations between 23 and 24 hours after administration (from Marshall and Fritz[33]).

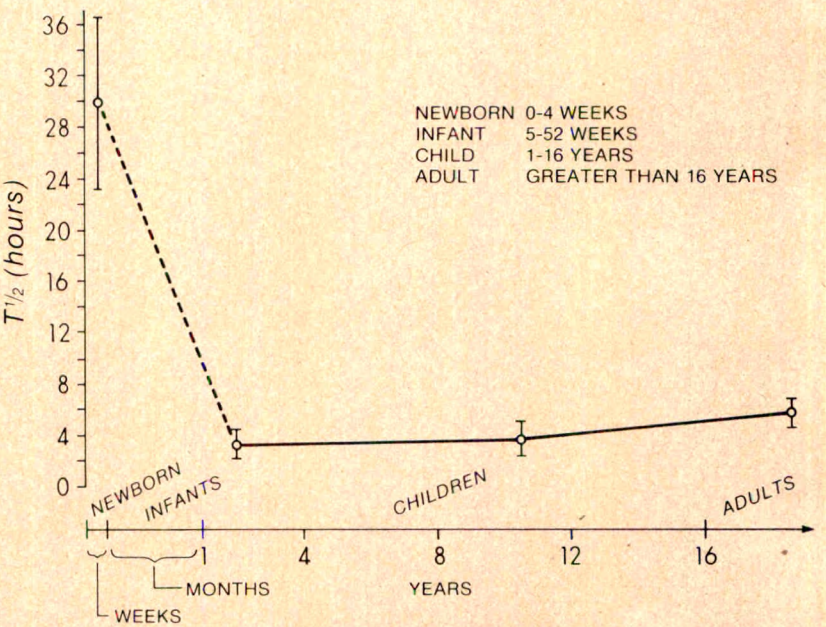


Fig 7.—Elimination half-time as function of age for theophylline (mean ± SD): newborn (3 to 15 days), 30 ± 6.5[21]; child (1 to 4 years), 3.38 ± 1.11[23]; child (6 to 16.75 years), 3.69 ± 1.13[34]; adult, 5.56 ± 1.46.[23]

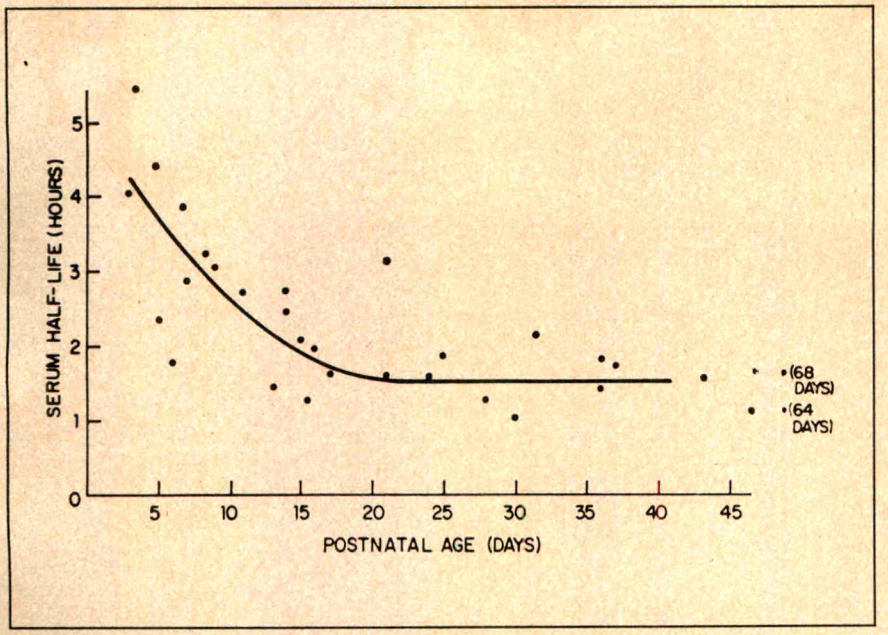


Fig 8.—Changes in serum ampicillin half-life with postnatal age (from Axline et al[26]).

penicillin,[27] gentamicin,[28] kanamycin,[29] amikacin,[30] tobramycin,[31] and other antibiotics.[32] Newborns less than 1 week of age require even smaller daily doses than those 2 to 4 weeks of age. After this crucial first month, renal elimination rates approximate those of older infants sufficiently that separate dosage schedules need not be applied. Full adult values for the GFR and tubular functions are reached by 5 to 7 months of age.

The physiologic factors that differ in newborns and older children that may affect a drug's pharmacokinetics, and therefore the patient's dosage requirements, are summarized in the Table.

KINETICS OF DRUG ELIMINATION

An understanding of the basic kinetics of drug elimination is essential for intelligent drug usage and for comparative pharmacology.

After complete absorption and distribution, with stabilization of the drug concentration, the amount of drug in the body is a function of the amount eliminated via metabolism and excretion. The rate of drug disappearance will reflect the sum total of the rates of drug metabolism and excretion.

Since drug absorption may continue for some time after oral, intramuscular, or subcutaneous dosing and complicate the analysis of elimination kinetics, it is simplest to examine drug disappearance after intravenous injection (Fig 3).[10 (pp20-21)] An initial rapid decrease in serum concentration occurs, reflecting drug distribution throughout the body. A more gradual decline, or elimination phase, then proceeds. For most drugs, elimination follows *first-order kinetics:* a constant *fraction* of the drug in the plasma is eliminated per unit time. The amount of drug eliminated per unit time is proportional to the amount of drug present, and will progressively decline as the amount of drug present decreases.

A graphic representation of the relationship that derives between changing drug serum concentration and time is helpful in visualizing the process. An arithmetic scale yields a curvilinear decay. Plotting on a semilogarithmic scale, with log plasma drug concentration vs time as the axes, yields a straight line for drug elimination. This reflects the constant *fraction* of total drug eliminated per unit time (Fig 5).[33]

Analysis of the straight-line relationship allows a derivation of the drug's elimination half-time; that is, the time required for elimination of half the amount present. The amount eliminated in one half-time is one half or 50% of the total, regardless of the absolute amount present. The derivation of the drug half-life, as a reflection of metabolic and excretory capacities, allows meaningful comparisons of drug elimination processes in different age groups. Drug dosage regimens are, in part, based on the elimination rate and, therefore, schedules will vary between children and adults.

There are some drugs that are handled by *zero-order kinetics,* with elimination that proceeds at a constant rate, independent of the drug serum concentration. In these cases, a constant *amount* of drug is eliminated per unit time. For these drugs, pathways available for elimination become saturated at a certain drug concentration. At higher concentrations the reactions proceed at a fixed rate, regardless of how much drug is present. As a result, once saturation occurs, the total amount of drug in the body will rise disproportionately as drug intake continues, with a significant risk of toxicity.

Important examples of substances handled in this manner are phenytoin, aspirin, and ethanol. They follow first-order elimination kinetics at low doses and serum concentrations but zero-order kinetics at higher doses and concentrations. Where the crossover in kinetics occurs is different for each person. Once above saturation, small dosage changes will lead to greater elevations in serum concentration than expected. At the "usual" doses of aspirin for antipyresis and analgesia and of phenytoin for seizure control, elimination should follow first-order kinetics.

Graphic representation of zero-order elimination with an arithmetic plot yields a straight line, since a constant amount decreases per unit time. With a semilogarithmic plot, a curvilinear decay results (Fig 6).[33]

One cannot derive an elimination half-time for drugs that follow zero-order kinetics since the apparent half-life will vary depending on the quantity of drug present. One can only calculate the amount of drug eliminated per unit time.

Despite the relative paucity of data on metabolism and excretion of many

agents in common usage, generalizations can be made regarding comparative rates of drug elimination in patients of different ages. For drugs eliminated via hepatic metabolism, the half-lives are prolonged in the neonatal period, reach a minimal level during late infancy and early childhood, and then gradually increase through adulthood (Fig 7). For drugs eliminated via renal excretion in the unchanged form, the inverse relationship between elimination rate and postnatal age stabilizes at about 1 month of age, and the half-life is fairly constant thereafter (Fig 8).[26]

Pediatric therapeutics can only benefit from the generation of additional data on the disposition of drugs in children. In 1969, the American Academy of Pediatrics Committee on Drugs reviewed the problem of the FDA regulations on safety and efficacy testing and, recognizing the pharmacologic individuality of the pediatric patient, suggested that, with certain qualifications, drug testing should be performed in children as well as adults. They concluded that "the design, recording and reporting of such studies is in the interest of the profession, the drug industry and, most importantly, the children."[35]

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Picture of the Month

Sydney S. Gellis, MD, Murray Feingold, MD; Contributed by
Juan F. Sotos, MD; Carolyn A. Romshe, MD; Edward A. Cutler, DO

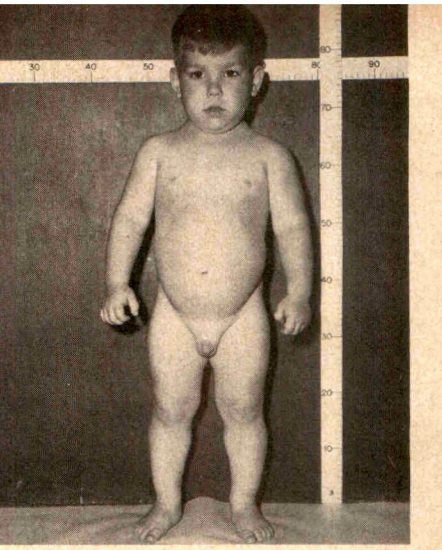


Fig 1.

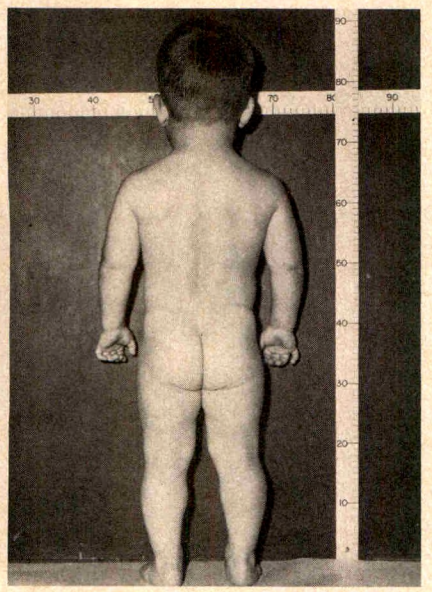


Fig 2.

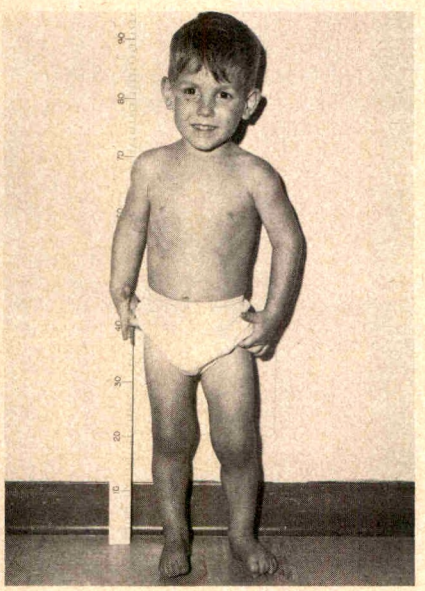


Fig 3.

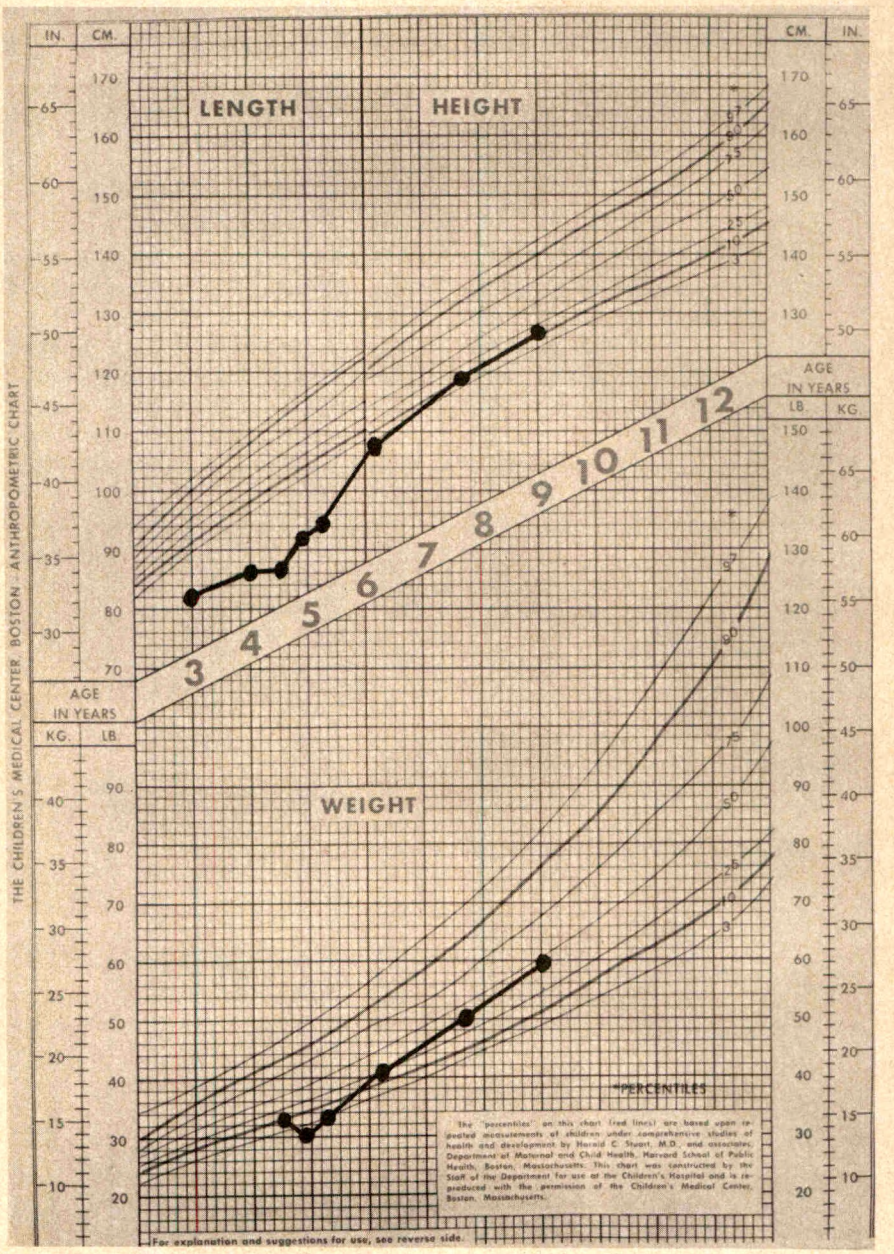


Fig 4.

From the Division of Endocrinology and Metabolism, Department of Pediatrics, College of Medicine, Ohio State University, and the Children's Hospital J. W. Champion Center, Columbus, Ohio.

Reprint requests to Boston Floating Hospital, 20 Ash St, Boston, MA 02111 (Dr Gellis).

Denouement and Discussion

Kocher-Debré-Semelaigne Syndrome

Fig 1.—Generalized muscle enlargement. Facies are not typical of hypothyroidism.

Fig 2.—Generalized muscle enlargement.

Fig 3.—Decrease in muscle size after treatment of hypothyroidism.

Fig 4.—Growth chart demonstrating substantial increase in height after initiation of thyroid treatment.

Manifestations

Kocher[1] first reported the association of generalized muscular "hypertrophy" and hypothyroidism; Debré and Semelaigne[2] subsequently noted the decrease in muscle size after thyroid therapy. Because of generalized muscle enlargement, especially of the calf muscles, patients with this syndrome usually have an athletic appearance.[3] The cause of the large muscles is not known and histopathological findings are not consistent.[4]

Other conditions in which muscles may appear enlarged are certain types of muscular dystrophy, hypertrophia muscularum vera, de Lange's extrapyramidal syndrome of muscular hypertrophy, familial periodic paralysis, lipodystrophy, and myotonia congenita. Large muscles are occasionally found in children with primary hypothyroidism and therefore it may be difficult to determine if these patients should be classified as having Kocher-Debré-Semelaigne syndrome, especially since the pathogenesis of the muscle enlargement is not known.

Genetics

An autosomal recessive mode of inheritance has been suggested.

Treatment

After treatment with levo-thyroxine decrease of the muscle size is noted.

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The Editors welcome contributions to "Picture of the Month" and "Radiological Case of the Month." Those who wish to contribute should send their manuscripts to Dr Gellis (Picture of the Month), Boston Floating Hospital, 20 Ash St, Boston, MA 02111, or Dr Young (Radiological Case of the Month), Department of Radiology, Children's Hospital of Pittsburgh, 125 DeSoto St, Pittsburgh, PA 15213. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.

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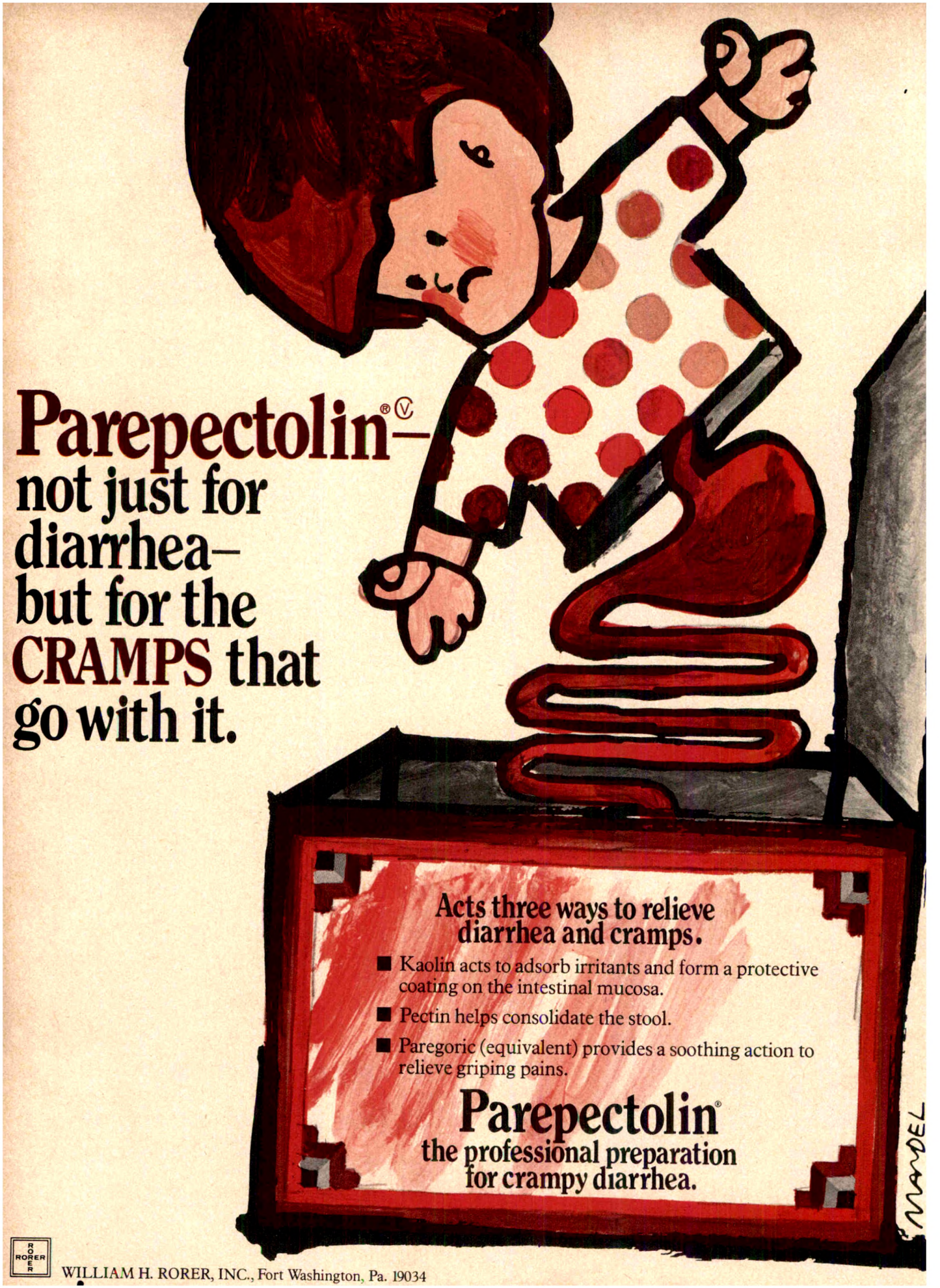
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Radiological Case of the Month

Lionel W. Young, MD
Contributed by Edwin E. Goldberg, MD, Jalayne Morrison

Clinical History.—A 45-year-old woman was admitted to the hospital for elective minor surgery. Her developmental milestones had been normal. She was moderately short and had fork-like deformities of both wrists. The abnormal configuration of her wrists was first noted at 12 years of age. A roentgenogram taken at that time is seen in Fig 1. She had no pain and had no restricted motion of her wrists. Her maternal grandfather and aunt had similarly deformed wrists and were noticeably shorter than her other relatives. At the age of 24 years, she was described as a "borderline dwarf." When she was 30 years old, hypothyroidism was diagnosed after five spontaneous abortions, all at about six weeks' gestation. She has been well controlled on levothyroxine sodium.

Physical Examination.—Her height was 135 cm (less than the third percentile). She showed the classical findings of mesomelic dwarfism with bilateral Madelung's deformity of the wrists (Fig 2). Wrist range of motion was entirely normal; the ulna could be reduced easily, but quickly resumed its subluxed position on removal of the slight pressure.

Values for complete blood cell count, serum electrophoresis, BUN level, creatinine level, serum electrolyte levels, serology, and urinalysis were normal.

Roentgenograms of the chest, skull, sella turcica, mandible, pelvis, and spine were normal. Roentgenograms of the forearms and wrists taken on admission are seen in Fig 3 and 4.

From the University of Illinois School of Medicine (Dr Goldberg and Ms Morrison), Peoria, and the Department of Internal Medicine (Dr Goldberg), Decatur Memorial Hospital, Decatur, Ill.

Reprint requests to Department of Radiology, Children's Hospital of Pittsburgh, 125 DeSoto St, Pittsburgh, PA 15213 (Dr Young).



Fig 1.

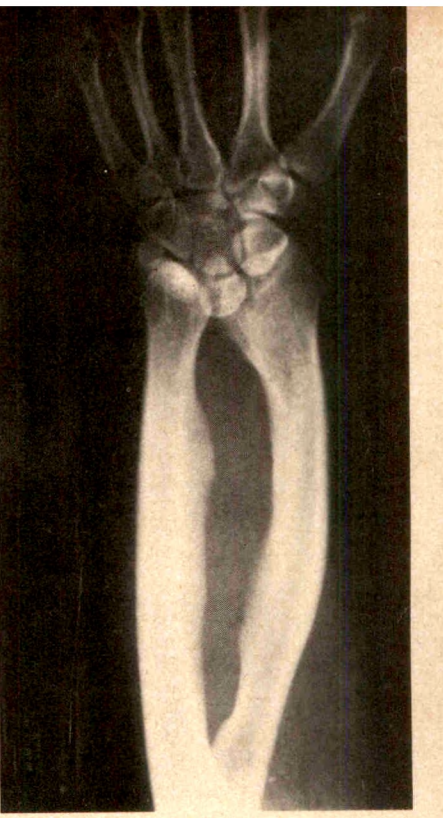
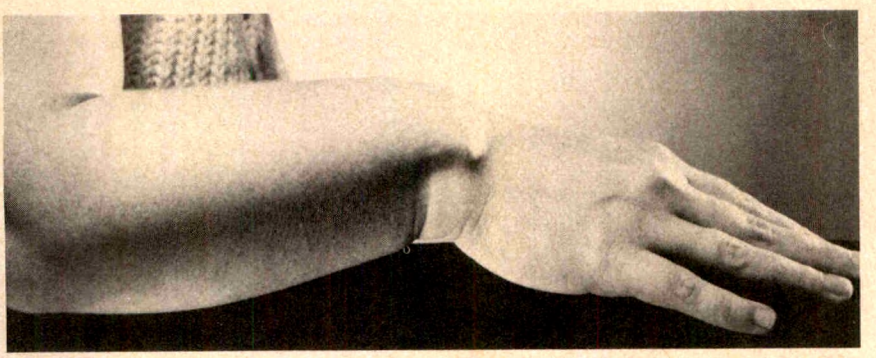


Fig 3.



Fig 4.

Fig 2.



Denouement and Discussion

Fig 1.—Right wrist deformity (posteroanterior roentgenogram) at 12 years of age. Note lateral bowing of radius. Carpal bones are wedged between deformed radius and ulna, giving them triangular shape with lunate at apex.

Fig 2.—Left wrist deformity (lateral view).

Fig 3.—Posteroanterior roentgenogram of wrist deformity at 45 years of age. Note progression of triangularization of carpus and extensive "fish-finning" of radius.

Fig 4.—Lateral roentgenogram of same wrist at 45 years of age.

Dyschondrosteosis

In 1904, Galliard and Levy[1] described a 28-year-old woman with mesomelic dwarfism and bilateral bayonette deformity of the wrists. A quarter of a century later, Leri and Weill[2] described a 25-year-old woman with an identical syndrome and they proposed the term "dyschondrosteosis" to describe it. Since that time, about 50 articles have appeared in the world literature reporting 37 cases that were very similar to the first two.[1,2] Leri and Weill,[2] in their report, emphasized two cartilaginous modeling abnormalities, brachymelic mesomelic dwarfism and bayonette deformity of the wrists. Since that time, most authors have used these two criteria as the hallmarks of the syndrome. In the early reports, dyschondrosteosis consisted of brachymelic mesomelic dwarfism (a moderate absolute shortening of both the proximal and middle segments of extremities, but with a greater degree of shortening of the middle segments, the leg and forearm) plus the bayonette deformity of the wrist first described by Madelung[3] in 1878. The trunk, skull, hands, feet, and pelvis were normal. In addition to these two basic criteria, other abnormalities have also been reported, including exostoses[2,4]; shortening of the femur, humerus, and metacarpal bones[4,5]; lateral subluxation of the patella[6]; genu varum[4,5]; thickening of long bones[7]; coxa valga[4]; and cubitus valgus.[4,8]

The term "dyschondrosteosis" has now evolved to describe many combinations of these abnormalities, but always with the two constant features of mesomelic dwarfism of a mild degree and Madelung's deformity of the forearms and wrists.

The age at which dyschondrosteosis is diagnosed is directly proportional to the degree of suspicion. This condition in small infants has been diagnosed roentgenographically when the investigator's suspicion was aroused by the fact that several other family members had the same condition. Usually, the condition has been recognized about the time of puberty, and then, as a result of abnormal wrist configuration.

It should be noted that the bayonette wrist abnormality must be diagnosed roentgenographically, although the moderately and severely affected individuals are easily recognized clinically. Lisker et al[10] and Langer[4] reported several cases that were clinically normal but that roentgenographically showed definite evidence of Madelung's deformity to varying degrees.

There seems to be general agreement that dyschondrosteosis is inherited as an autosomal dominant trait. The syndrome is much less commonly reported in males; 75% of the cases reported are females.[6,8,10]

For many years, the syndrome named after Leri and Weill[2] was the only known form of disproportionate shortening of the middle segments of the extremities, ie, mesomelic dwarfism. Therefore, it does not seem unusual that the term mesomelic dwarfism became synonymous with dyschondrosteosis and the Leri-Weill syndrome. However, in recent years, other forms of dwarfism have been reported with preferentially short middle segments of both upper and lower extremities.

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Haemophilus influenzae Sepsis in the Premature Infant

Haemophilus influenzae has been reported infrequently as a cause of serious illness in the neonatal period.[1-4] We have identified six infants with neonatal *H influenzae* sepsis since 1975, all of whom demonstrated a fulminant clinical course similar to early-onset group B streptococcal sepsis. Review of bacteriology records from the previous ten years disclosed only one additional case of neonatal *H influenzae* sepsis. The present report is a review of these cases with the purpose of identifying factors present shortly after birth that may provide for early diagnosis and treatment.

Report of a Case.—This 1,288-g, 29 weeks' gestation boy was born Nov 23, 1975, to a 27-year-old, gravida 3, para 2 mother. Membranes ruptured seven hours prior to delivery. Late decelerations were noted on the monitor prior to delivery; Apgar scores were recorded as 1 and 6 at one and five minutes, respectively. The infant was transferred to Children's Mercy Hospital, Kansas City, Mo, at 1½ hours of age because of respiratory distress and was placed on a respirator shortly after admission. Bacterial cultures were obtained and intravenous therapy with aqueous penicillin and gentamicin was started at 5 hours of age. The initial WBC count at 4 hours of age was 1,600/cu mm, with 4% neutrophils and 96% lymphocytes. Roentgenographic findings were typical of hyaline membrane disease without evidence of pneumonia. The infant's condition rapidly deteriorated, and he died at 12 hours of age. Autopsy showed hyaline membrane disease and intraventricular and paraventricular subarachnoid hemorrhage. *Haemophilus influenzae*, nontypable, was isolated from the blood culture.

Laboratory Methods.—Blood cultures were obtained prior to death, following skin preparation with iodine and alcohol. After incubation for 24 hours in tryptic soy broth, the specimen was subcultured on chocolate agar incubated in carbon dioxide. Broth and plates were observed daily for seven days. Positive identification of *H influenzae* was made by Gram stain, colony morphology, and requirement for the V and X factors as shown by a Haemophilus Identification Quad Plate. Serotyping of *H influenzae* strains was done by the Missouri State Laboratories.

Cerebrospinal fluid was collected on each infant. Peripheral cultures were obtained from swabs of the nose, throat, ear canal, umbilicus, and rectum. Cerebrospinal fluid and external swabs were immediately inoculated on sheep blood and chocolate agar. Plates were read at 24 and 48 hours and colonies identified as just described.

Results.—Clinical data from the seven infants are summarized in the Table. All were preterm; five were 30 weeks' gestation or less. Symptoms of respiratory distress were present from birth in six of the seven cases. The remaining infant (case 1) developed respiratory distress, lethargy, and feeding problems at 20 hours of age. This was the only infant in whom a positive culture of the CSF was obtained. Prolonged rupture of membranes (more than 12 hours) was present in only one case, and occurred within one hour of birth in four cases.

Six of the seven infants died. Each had a fulminant course of increasing respiratory distress, hypoxia, and metabolic and respiratory acidosis unresponsive to therapy. A roentgenographic picture of hyaline membrane disease, but not pneumonia, was present in five. The sixth infant had a normal chest roentgenogram (case 5). All six patients required ventilator support prior to death. Two infants (cases 2 and 4) died prior to receiving antibiotics.

Clinical and Laboratory Data From Infants With Neonatal *Haemophilus influenzae* Sepsis

Case	Gestational Age, wk	Duration of Rupture of Membranes, hr	Isolate Source	*H influenzae* Serotype	Total WBCs/cu mm	Absolute No. of Polymorphonuclear Leukocytes	Absolute No. of Band Forms	Antibiotics	Outcome
1	30	0	CSF, blood	f	3,000	300	0	+	Died at 36 hr
2	27	48	Blood	Unknown	7,000	3,780	140	—	Died at 34 hr
3	29	7	Blood	Not typable	1,600	16	32	+	Died at 12 hr
4	30	0.5	Blood, throat	Unknown	1,500	0	0	—	Died at 13 hr
5	34	10	Blood, throat	c	2,800	504	336	+	Died at 45 hr
6	37	1	Blood, throat	b	2,700	81	378	+	Lived
7	29	0.75	Blood	d	800	8	0	+	Died at 28 hr

Autopsies were performed on all six of the deceased infants. Hyaline membranes were present in four cases. Pneumonia, which had not been suspected from roentgenographic findings, was present at autopsy in one patient (case 5). Sensitivity testing was done on five of the seven organisms isolated. All were sensitive to ampicillin and gentamicin.

Total WBC count obtained at varying times were uniformly low, with a predominant finding of neutropenia. The one survivor, whose initial WBC count was 2,700/cu mm, with 3% neutrophils and 14% band forms, had a marked increase in the absolute neutrophil count as he improved. At three days, the total WBC count was 21,400/cu mm, with 60% neutrophils, 9% band forms, and 31% lymphocytes.

Comment.—Several other reports of neonatal *H influenzae* sepsis have appeared in the literature.[1-5] A recent report by Bales and Watkins[4] suggests the possibility that a fulminant form of neonatal *H influenzae* sepsis

very similar to early-onset group B streptococcal sepsis may be appearing.[4] Our data support this observation. In contrast to their cases, we did not find pneumonia to be a predominant clinical or roentgenographic finding. However, *H influenzae* sepsis, like group B streptococcal sepsis, appears to be very difficult to distinguish from hyaline membrane disease and may coexist with it.[6] No specific serotype appears to be predominant in this early-onset disease.

Some investigators have found a high incidence of prolonged rupture of the membranes (greater than 12 hours) in *H influenzae* sepsis.[1,2] However, our data indicate that prolonged rupture is not a prerequisite for infection to occur. Initiation of antibiotics within several hours following the onset of symptoms did not appear to have a beneficial effect on outcome. This has also been observed with early-onset group B streptococcal sepsis.[7]

Leukopenia, especially neutropenia, was a striking finding in all our patients. This is an important finding in the diagnosis of overwhelming sepsis. There is often a sudden reduction of neutrophils in the circulating blood of septic infants due to removal of injured cells.[8] Lymphocytes thus predominate, and the absolute number of segmented and band forms is decreased.

The most likely source of colonization of the infants is from flora present in the birth canal. Three of the seven infants had *H influenzae* isolated from the throat, providing indirect evidence of mother-to-infant transmission. The data of Khuri-Bulos and McIntosh[1] support this hypothesis. Placenta, amniotic fluid, urine, or cervix yielded positive cultures in all eight of their cases. We did not pursue maternal vaginal and cervical cultures in our population because of adverse psychological effects observed in mothers during earlier studies on the etiology of group B streptococcal colonization.[9]

Recent reports indicate that the incidence of *H influenzae* sepsis is increasing as an important cause of early-onset neonatal disease.[1-4] The very premature infant is particularly vulnerable when infected. It is likely that prevention of *H influenzae* neonatal sepsis in the future will involve diagnosis and treatment of the colonized mother or protection of the fetus with transplacental antibody. In the interim, the possibility of *H influenzae* sepsis in the preterm infant with respiratory distress should be strongly considered. Blood culture, complete blood cell count, and clinical assessment are indicated. Early initiation of antibiotic therapy with ampicillin and an aminoglycoside is recommended in infants who demonstrate leukopenia of less than 10,000/cu mm or other findings suggestive of sepsis.

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Dural Sinus Thrombosis in Leukemia

Neurologic signs and symptoms in acute lymphocytic leukemia are often secondary to CNS leukemia.[1] Cerebrospinal fluid pleocytosis is usually present in such cases.[1] Dural sinus occlusion is a rare complication of CNS leukemia and may produce neurologic signs and symptoms without CSF pleocytosis.[2] We recently evaluated a patient with acute lymphocytic leukemia in bone marrow remission. Signs and symptoms of CNS leukemia developed in this patient, without CSF pleocytosis. There was occlusion of the superior sagittal sinus and other major venous channels but no evidence of infection or CNS leukemia. This seems to be a unique occurrence.

Report of a Case.—The condition of a 6-year, 3-month-old boy was evaluated on Dec 9, 1977, for lethargy and headache. He was first seen at the University of Wisconsin Hospitals, Madison, at age 5 years for abdominal distension, fever, and drowsiness. Peripheral WBC count was 45,900/cu mm, with 60% lymphoblasts, and the bone marrow was completely replaced by lymphoblasts. More than 80% of peripheral blood lymphoblasts spontaneously formed sheep cell rosettes consistent with T-cell leukemia. Results of a CSF examination were normal. The patient was successfully induced into bone marrow remission and received cranial irradiation and intrathecal methotrexate.

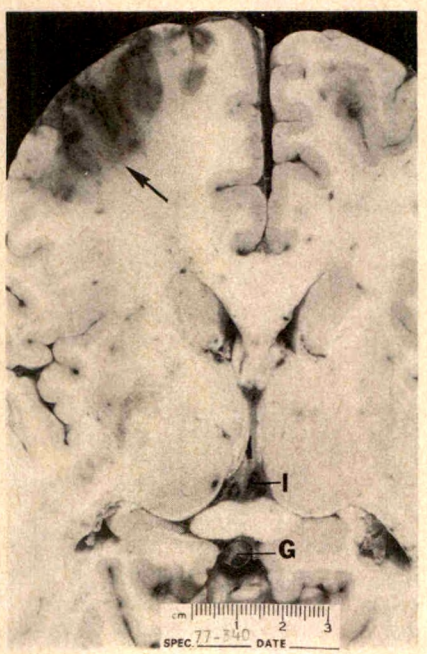
The child did well until Oct 5, 1977, when enlarged testicles developed. Bone marrow aspiration showed replacement with lymphoblasts. The CSF contained no cells. Prednisone and vincristine sulfate therapy was started. The patient also received asparaginase (L-asparaginase) for three weeks and was given 2,400 rads to both testicles. Bone marrow remission was achieved in three weeks. Therapy was continued with vincristine, doxorubicin hydrochloride (Adriamycin), cytarabine (cytosine arabinoside), and prednisone. The patient was also to receive asparaginase three times a week for a total of nine additional doses. Eight days after the child achieved bone marrow remission, headache and drowsiness developed. Examination was unremarkable except for lethargy, and results of CSF studies were normal. He received his weekly vincristine and the 15th dose of asparaginase. The following day (Nov 10, 1977) he had three generalized tonic-clonic seizures. Results of a physical examination were unchanged. Findings from laboratory studies, including blood glucose, serum electrolytes, and complete blood cell count (CBC) with differential, were normal. Prothrombin time was 12.4 s (control, 12 s), partial thromboplastin time was 30 s (control, 34 s), and there were 230,000 platelets per cubic millimeter. CSF showed no cells, and protein and glucose levels were normal. Phenobarbital therapy was begun, and asparaginase was discontinued. Three generalized seizures occurred during the ensuing 24 hours, followed by a flaccid left hemiparesis. An EEG showed diffuse slowing, more severe over the right hemisphere. Technetium Tc 99m sulfur colloid brain scan showed increased activity in the left frontal area, and computerized tomography showed a crescent-shaped area of decreased density in the rostral portion of the left frontal lobe. Results of a bone marrow examination were normal, and repeated CSF studies showed no cells with normal protein and glucose. A presumptive diagnosis of CNS leukemia was made, and the patient was given 1,400 rads of cranial irradiation in seven doses. On Nov 20, he complained of severe head, neck, and back pain. He progressively

became more obtunded and died five days later.

Pathologic Condition.—On gross examination, the brain showed occlusion of the entire superior sagittal sinus by an organizing thrombus. Superficial cerebral veins draining the left frontal region were occluded by old clot. Recent thrombus was present in the great vein of Galen, internal cerebral veins, and lateral sinuses (Figure). The left frontal region contained a hemorrhagic infarct (Figure). Infarction of the superficial grey matter was also noted in the right central parasagittal region. Microscopic examination showed organization of the superior sagittal sinus thrombus consistent with an age of 2 to 3 weeks. The left frontal infarct showed hemorrhage, mild astrocytosis, and glitter cells indicating a lesion of similar duration. The right central infarct showed similar changes and was thought to be about 10 to 14 days old. There were no signs of leukemic infiltration or infection. The general autopsy showed no evidence of leukemia, and the bone marrow was normal.

Comment.—Dural sinus thrombosis is rare in the patient with leukemia.[2] David and co-workers[2] recently described a 7-year-old boy in whom dural sinus occlusion developed while he was in bone marrow relapse. Lymphoblastic infiltration of the walls of the superior sagittal sinus was also found, and tumor cells were seen within the thrombus.

Horizontal section of brain showing swollen left frontal lobe with hemorrhagic infarct (arrow) and thrombosis of internal cerebral veins (I) and great vein of Galen (G).



In contrast, irritability, lethargy, and later, a left hemiparesis developed while the patient was in remission. Despite normal results of CSF examinations, we felt that our patient had lymphoblastic infiltration of the cerebrum with a left hemiparesis secondary to vascular occlusion. Since CNS relapse is a frequent complication of T cell leukemia,[3] radiation therapy was initiated. However, neuropathologic examination and an extensive general autopsy showed no evidence of CNS or systemic leukemia. The death of our patient may have been related to complete dural sinus occlusion, with the initial pathologic process beginning several weeks earlier.

Thrombosis or major venous channels in leukemia has been attributed to leukostasis, chemotherapy, mycotic infection, and infiltration by tumor cells.[2] Leukostasis within cerebral vessels and nodules of leukemic cells have been found in patients dying of acute leukemia who have high peripheral WBC counts.[4] These collections of cells may result in thrombosis or cause instability of the vessel wall and subsequent hemorrhage.[4,5]

The failure to find tumor cells on neuropathologic examination in our patient's case argues against infiltration of vessel walls by tumor cells as the cause of venous occlusion. However, the possibility that cranial irradiation eradicated histologic evidence of CNS leukemia cannot be excluded.

Some of our patient's symptoms could have been secondary to chemotherapy. Neurologic complications from doxorubicin hydrochloride, cytarabine, and prednisone are apparently rare, and acute neurologic problems related to vincristine have been reported in only a small number of patients during induction therapy.[6] However, somnolence, disorientation, seizures, and EEG abnormalities are not uncommon in patients receiving asparaginase therapy.[7,8]

It is also possible that chemotherapeutic agents played a role in initiating our patient's venous thrombosis. It is known that asparaginase can effect the synthesis of clotting factors.[9] Abnormal clotting, decreased plasminogen, and elevated fibrin degradation products have been noted in patients receiving asparaginase therapy. Coagulopathy has also been reported with vincristine and prednisone.[10] Although our patient's prothrombin time and partial thromboplastin time were normal when his neurologic symptoms became evident, more sophisticated clotting studies might have shown abnormal results.

Our experience indicates that dural sinus occlusion with venous infarction may occur in the patient with leukemia while he is in remission. Signs and symptoms in such a patient may suggest CNS leukemia. Pathologic examination in our patient failed to show tumor cells, thus suggesting that thrombosis of major venous channels in the CNS may occur in the absence of peripheral or CNS leukemia.

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Nonproprietary Names and Trademarks of Drugs

Vincristine sulfate—*Oncovin.*
Asparaginase—*Crasnitin.*

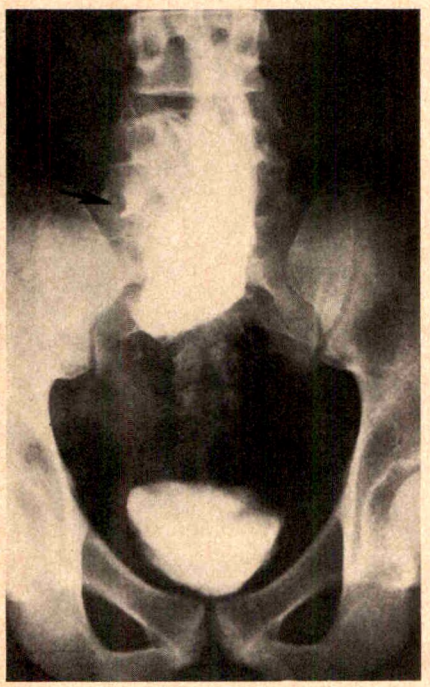
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Pelvic Kidney: Contraindication to Herniography

Sir.—Contrast herniography is well established as a method for demonstrating patency of the processus vaginalis. Although some contraindications have been stated in the literature, we report, to our knowledge, the first instance of an inadvertent "renal biopsy" due to a pelvic kidney.

Report of a Case.—A 20-year-old man was seen after being denied a job because of an inguinal hernia. On physical examination, no inguinal hernia was found, but the patient was noted to be hypertensive (158/102 mm Hg). Abdominal examination showed no masses. A herniogram was attempted.

Anterior abdominal wall was prepared in a sterile manner; a needle was introduced in the midline, 2 to 3 cm below the umbilicus, and contrast media was injected under fluoroscopic control. On the initial attempt, it was noted that the contrast agent was being injected into soft tissue. A second attempt was made with similar results and the examination was terminated.



Abdominal film taken while patient was in a supine position showing contrast media within anterior abdominal wall and bladder. Arrow indicates contrast-filled calyceal system.

Subsequently, hematuria developed. On subsequent follow-ups for hypertension, multiple physical examinations failed to show any evidence of an abdominal mass even though an intravenous pyelogram showed a pelvic kidney. In retrospect, this pelvic kidney was identified on the herniogram film (Figure). A renal arteriogram, 15 months after the herniogram, showed approximately 20% stenosis of the artery to the upper pole of the pelvic kidney, but no abnormality of the renal parenchyma was identified.

Comment.—Avery et al[1] and Kuhn[2] have recently reviewed their experience with herniography (contrast peritoneography). Their study substantiates the value of the technique for diagnosing occult hernias. Both studies indicated potential complications and contraindications, but do not raise the possibility of an inadvertent renal biopsy. Eckstein[3] indicates that pelvic kidneys are a "comparatively common malformation." The fact that this kidney was not palpated by numerous examiners, both before and after it was known to exist, adds to the potential risk.

As pointed out by Kuhn[2] abdominal roentgenograms taken 45 minutes after instillation of contrast media into the peritoneal cavity will provide excellent visualization of the kidneys due to absorption, circulation, and excretion of the agent. In our case, the film was obtained less than ten minutes postinjection, establishing the fact that visualization of the collecting system resulted from direct injection in the renal substance rather than from absorption of the contrast agent.

Although herniography remains a rather innocuous examination, pelvic kidney should be added to the previously described contraindications for this procedure.[2] The need to review previous intravenous urograms and for careful palpation of the periumbilical area by the individual performing the study should be stressed. When doubt persists, abdominal ultrasonography or intravenous urography to exclude a pelvic kidney or other abdominal mass may be indicated.

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Multiple Thromboemboli

Sir.—Smith and Blum (*Am J Dis Child* 132:294-295, 1978) described multiple thromboemboli staining for DNA in a child dying suddenly and unexpectedly after institution of chemotherapy for relapsing acute lymphocytic leukemia (ALL). We should like to describe a similar case and to suggest a possible mechanism for the fatal response.

Report of a Case.—Our patient was a 6¾-year-old girl with non-B, non-T-cell ALL. Her first remission was successfully induced with prednisone and vincristine sulfate, after which she received 2,400 rads of whole brain irradiation plus intrathecal methotrexate. The remission was maintained with 6-mercaptopurine, methotrexate, and cyclophosphamide. Eleven months after her diagnosis, a bone marrow relapse developed. Reinduction therapy consisted of prednisone, vincristine, and daunomycin. Three hours after the first injection of the latter two agents, she was noted to have a temperature increase to 39.4 °C. Thereafter, she became restless with signs of progressive respiratory distress. A chest roentgenogram documented signs of pulmonary edema. Respiratory compromise worsened despite attempts to improve ventilation, and the patient died six hours after her first injection of daunomycin.

A postmortem examination showed pulmonary edema. Microscopically massive quantities of nuclear and cytoplasmic debris as well as homogenous basophilic clumps stained for DNA with Feulgen reagent were identified in the small arteries, arterioles, and capillaries of the adrenals, kidneys, pancreas, bone marrow, and

lungs. These intravascular deposits were thought to represent lysed tumor cells.

Comment.—Of potential importance is the fact that the patient was heterozygous for glucose-6-phosphate dehydrogenase (G-6-PD) (2.96 IU/g Hb). Daunomycin and its congeners, in addition to binding with DNA, generate active oxygen metabolites within cells. The cardiomyopathy resulting from doxorubicin hydrochloride (Adriamycin) may be mediated by oxidative damage.[1] Moreover, RBCs exposed to doxorubicin hydrochloride contain oxygen metabolites and develop increased hexose monophosphate shunt activity.[2] If our patient's disease was the result of leukemic transformation of a lymphocyte clone in which the normal X-chromosome was inactivated, one might reason that her tumor would be exquisitely sensitive to oxidative stress because of deficient G-6-PD activity. Were this the case, daunomycin would be expected to induce massive tumor lysis, overwhelming clearance mechanisms for intravascular cellular debris and DNA.

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Nonproprietary Names and Trademarks of Drugs

Doxorubicin hydrochloride—*Adriamycin.*
Vincristine sulfate—*Oncovin.*

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Meconium Plug Syndrome, Cystic Fibrosis, and Exocrine Pancreatic Deficiency

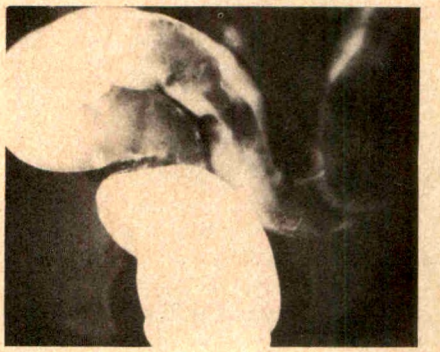
Sir.—We read with interest in the JOURNAL (132:167-169, 1978) the report by Rosenstein concerning the occurrence of the meconium plug syndrome (MPS) in three infants who later proved to have cystic fibrosis (CF). The association of MPS and CF was noted to have been previously reported in only one patient.[1] The more widely recognized association of MPS has been with Hirschsprung's disease.

We have observed severe MPS in a newborn infant who was found during the neonatal period to have extensive exocrine pancreatic deficiency. Cystic fibrosis was excluded by several sweat chloride tests.

Report of a Case.—At 12 hours of age, an infant (1,840 g, 39 weeks' gestation) began vomiting bile-stained fluid, and at 36 hours of age, developed moderate abdominal distention and passed a 10-cm-long solid meconium plug (first stool) after stimulation with a rectal thermometer. An abdominal roentgenogram showed ileus secondary to organic or mechanical obstruction to the distal large bowel. A barium enema (Figure) showed a long, lucent filling defect starting at the sigmoid colon and extending along most of the large bowel, indicative of a meconium plug. This study was followed by repeated isotonic saline-5% acetylcysteine (Mucomyst) enemas that yielded several small meconium plugs. Aqueous extracts of the plugs were strongly positive for protein when reacted with trichloroacetic acid.

The infant remained obstructed and was treated with nasogastric suction, intravenous fluids, and acetylcysteine enemas. On the fifth hospital day, a diatrizoate meglumine (Gastrografin) enema yielded persistent meconium plugs. Immediately thereafter, the patient passed a 10-cm-long, firm meconium plug and then several tenacious meconium stools. The abdominal distention subsided and feedings were well tolerated on the eighth day of life. Duodenal intubation was performed at 2 weeks of age; the patient was found to have no trypsin, chymotrypsin, carboxypeptidase, lipase, or amylase activity. Results of sweat tests (repeated four times) were normal. Enzyme studies and sweat tests repeated at 2 and 12 months of age confirmed the original results. Since the neonatal period, the patient has shown good response to pancreatin therapy and dietary management.

Comment.—While noting that others have attributed MPS to impaired colonic motility or intrinsic abnormalities of the meconium, Rosenstein appropriately concluded that the etiology of MPS is unclear. Our observations of MPS in a patient with exocrine pancreatic deficiency suggests that the MPS observed in the CF patients reported by Rosenstein is probably caused by pancreatic deficiency. The MPS in Hirschsprung's disease is presumably due to mechanical factors rather than enzyme deficiency. The frequent occurrence of



Barium enema shows filling defect of colon, indicating meconium plug.

meconium ileus in CF and the rarity of MPS in CF is curious, since they may be different manifestations of the same pathologic process. Conceivably, MPS may occur with total absence of pancreatic enzymes (as in our patient and in a few patients with CF). Low levels of enzymes in CF may limit expression to meconium ileus. Rosenstein has suggested that "all infants with the MPS be evaluated for the possibility of both Hirschsprung's disease and CF." We wish to suggest the evaluation of exocrine pancreatic function in these patients even if CF has been excluded by sweat tests.

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In Reply.—The case described by Townes and Kopelman is of interest in that it suggests that isolated exocrine pancreatic deficiency may be a cause of the meconium plug syndrome (MPS). On the basis of this observation, the authors suggest that the MPS seen in our patients with cystic fibrosis (CF) was likewise probably due to pancreatic deficiency. Although I agree with their speculation that the MPS and meconium ileus (MI) "may be different manifestations of the same pathologic process," there is conflicting, albeit fragmentary, data suggesting that exocrine pancreatic deficiency may not be the sole cause of meconium obstruction in

CF. There is little documentation of normal exocrine pancreatic function in infants with CF and MI, but there are rare anecdotal references to such cases.[1] Several investigators have suggested that MI may be the result of abnormal protein and mucoprotein secretions by the intestinal goblet cells and not from lack of pancreatic enzymes alone. Thomaidis and Arey[2] noted that, histologically, pancreatic involvement was mild in infants with MI, but that there was severe involvement of the intestinal glands of the small bowel. Oppenheimer and Esterly[3] carried out a morphologic study of 37 infants with CF and a history of MI. In ten of these cases, there were no pancreatic lesions. Most had widespread mucus gland hyperplasia of the intestinal tract. While these observations suggest that exocrine pancreatic deficiency may not play a major role in all instances of meconium obstruction, it is important to note that there may be little correlation between the histologic appearance of the pancreas and exocrine function.

It is clear that in order to increase our understanding in this area, exocrine pancreatic function needs to be carefully evaluated in infants with any type of meconium obstruction.

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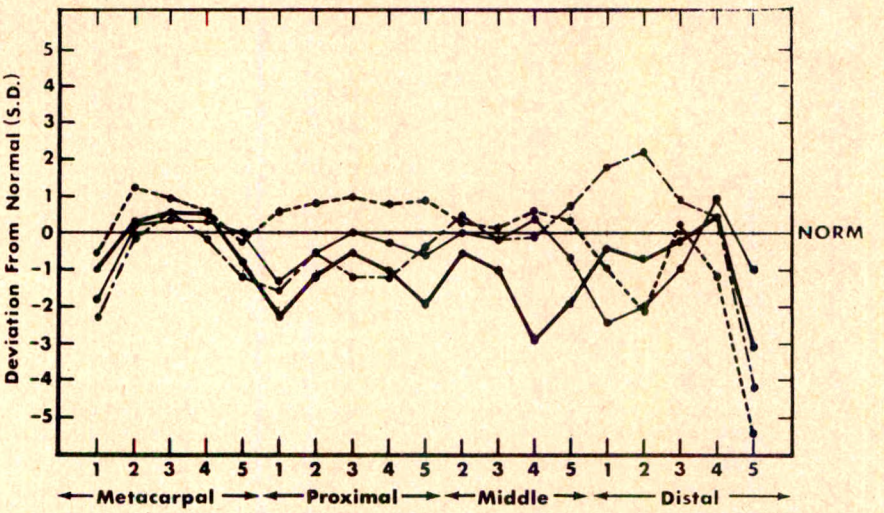
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Coffin-Siris Syndrome

Sir.—We were interested in the report in the JOURNAL (132:393-395, 1978) by Tunnessen et al on Coffin-Siris syndrome. During the past two years we have seen three cases suggestive of this condition.

Report of Cases.—A 4-year-old boy was severely microcephalic but lacked any nail abnormalities. His 3-year-old sister had markedly hypoplastic toenails. Both siblings had coarse facial features, short stature, and mental retardation. Their hand pattern profiles were similar to those of two of the original cases reported by Coffin and Siris (Figure).[1] Their mother appeared to be mentally retarded, and the father had an unusually small head and was of less than average mental ability.

The third patient lacked the characteristic facial features but had absent nails with hypoplasia of the terminal phalanges of the fifth digits. She was born prematurely, but her size was appropriate for gestational age. Mild feeding difficulties were present in infancy, and recurrent respiratory infections have persisted throughout early childhood. Postnatal growth has been very slow. At age 9½ years she weighed only 21 kg and was 118 cm tall (both values are below the third percentile). Head circumference was at the third percentile, but she was intellectually normal (IQ of 101 on the Stanford-Binet test). This child's hand pattern profile also correlated well with that of Coffin and Siris' two patients. All three of our patients had normal karyotypes. In the third patient, a detailed endocrinological evaluation gave normal findings.



Hand pattern profiles of patients with Coffin-Siris syndrome. Solid lines indicate patients studied by us. Broken lines refer to two of original patients of Coffin and Siris. Similarity exists in these patient's pattern profiles with exception of first, second, and third distal phalanges.

Comment.—The occurrence of this syndrome in two siblings raises the possibility of recessive inheritance. Neither of the parents exhibited similar clinical findings except that they both were intellectually deficient. Comparison of our patients with those reported by Senior[2] suggests that the findings in these patients are more compatible with the Coffin-Siris syndrome. Senior's patients were all short at birth and their facial features were quite dissimilar from those observed in our patients. Two of our three patients were significantly retarded, while the intellectual deficit in Senior's syndrome is borderline. All three of our patients were microcephalic. In view of our third patient's normal intellectual development, it is interesting that the patient reported by Smith[3] with absent fifth fingernails and short stature was also of average mental ability. It would appear that either the spectrum of clinical findings in this syndrome is much wider than previously recognized or the Coffin-Siris syndrome is a heterogenous entity. We believe that hand pattern profile analysis may be of use in diagnosing borderline cases.

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Infectious Mononucleosis

Sir.—I was interested to see in the JOURNAL (132:78-86, 1978) the recent review of infectious mononucleosis by Rapp and Hewetson. A few years ago in the JOURNAL (128:239-243, 1974), we reported a fatal case of infectious mononucleosis in a child who was an exception to some of the remarks made by Rapp and Hewetson. Our

patient was only 2 years old but had heterophil titers (unadsorbed) as high as 1:1,792. He subsequently developed Reye's syndrome, not to our knowledge previously described and not mentioned by Rapp and Hewetson as either a neurologic or hepatic complication. Remarkably, he recovered from the Reye's syndrome but then fell victim to granulocytopenia, a complication of infectious mononucleosis that Rapp and Hewetson did describe. However, he died in septic shock, in spite of vigorous intravenous antibiotic treatment. The hematologic complications of infectious mononucleosis may be transient and reversible, but they are not necessarily benign.

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Children of Incest: When To Suspect and How To Evaluate?

Sir.—We welcomed the articles in the February 1978 JOURNAL (132:124, 1978) concerning incest because they alert the pediatrician to a relatively common problem that tends to be handled poorly by the physician. Dr Adams' editorial raised the concern about the deleterious consequences of incestuous matings in which the risk for congenital abnormalities and mental retardation approaches 30% to 40%.

We would like to alert physicians to an observation we have made, which is that one should suspect incest when a young, unmarried mother does not clearly identify the father of her baby. The children of unmarried teenagers frequently become available for adoption. In our experience, a surprisingly large number of adopted children have autosomal recessive diseases, raising the possibility of incest. Recently, we have evaluated two unrelated, adopted children, each with two, different, rare recessive disorders, making it likely that they are the products of consanguineous or incestuous matings. In a third case, a child was diagnosed to have a rare type of dwarfism (Langer's mesomelic dwarfism, caused by homozygosity for a gene that manifests in carriers as dyschondrosteosis, presenting with mild short stature, short forearms, and Madelung's deformities). The child was born to an unmarried teenager who together with her brother and mother were affected with dyschondrosteosis (ie, carriers for Langer's mesomelic dwarfism). The diagnosis of an autosomal recessive condition in the child allowed the recognition of the presence of incest in this family.

We have followed five children who are the products of brother-sister matings over the past year. These children would normally be made available for adoption, but because of the known high incidence of mental retardation and congenital malformations, we raised the question of whether there would be a way to screen these children for genetic disorders, congenital malformations, and developmental delay, so that potential problems could be identified for the adoptive parents. We developed a protocol and have followed these children during infancy with the idea that if the tests are negative and the child is developmentally normal at the end of a year, the risk of an undetected congenital malformation or more than mild mental retardation appearing in the future would be substantially decreased. Our program includes the following: complete physical examination and developmental assessment at three-month intervals, urinary amino acids screening, sweat chloride test, ophthalmologic examination, audiometrics, skeletal roentgenograms, IVP, banded karyotype, CBC count, urinalysis, and formal psychometric testing at 1 year of age. We would welcome further suggestions for this type of evaluation.

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Incest

Sir.—The article on incest by Weitzel et al (132:127-130, 1978) and the editorial comment by Weiner (132:123-124, 1978) in the February 1978 issue of the JOURNAL are welcome additions to the scanty and perplexing literature on child sexual abuse. I agree that "knee jerk responses" may be detrimental, ie, immediate removal of the child. The symptom of incest warrants careful evaluation and planning. Both authors are clear to point out that the studies used to support allegations that sexual abuse of children is damaging are biased and select for children already identified as disturbed. However, the data used to support the contention that sexual abuse may not be harmful are equally misleading[1,2]; both deal with an inpatient psychiatric population. Those authors' perceptions of the severity of damage seem open to question.

At this point, we honestly don't know what the acute and long-term effects of child sexual abuse are, and until long-term follow-up studies are funded, we won't. In the meantime, however, it would seem unwise to assume that there are no effects, and one must plan an individualized intervention that will assure that the child will no longer be *victimized* by the adult. As Drs Weiner and Weitzel pointed out, this intervention may take a variety of forms.

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Amphotericin B and Maduromycosis

Sir.—Let me react to the CLINICAL MEMORANDUM on the treatment of Maduromycosis with amphotericin B by Hayden et al in the JOURNAL (131:927, 1977). We would point out that our case, to which they refer in their third reference, also had "apparent remission," but recurred thereafter. I believe strongly that the word "cure" is usually inappropriate in chronic fungal disease, and certainly so if only short-term follow-up is available. For Hayden and his colleagues, as for us, intra-articular administration of amphotericin B was "something to do." I doubt very much that it was considerably better than the policy of no action whatsoever. I would refer the interested reader to our article on coccidioidal arthritis[1] for yet another look at how imperfect is our treatment of chronic fungal disease by amphotericin B, whether by the topical or intravenous route.

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The Mongoloid Child: Recognition and Care, by Christof Wunderlich, translated and edited by Royal L. Tinsley, Jr, Thomas R. Harris, and Dorothy I. Marquart, 184 pp, $12.50 ($5.95 paper), Tucson, University of Arizona Press, 1977.

Christof Wunderlich's book, *The Mongoloid Child*, mixes precise, established fact with his poetic license as an author and his deep feelings as the father of a youngster with Down's syndrome. While this sensitive combination serves him in good stead in his description of the role of the physician in the care of a child with Down's syndrome, it serves as a deterrent when he utilizes unproved medical means to assist the family in the growth and development of the child. He advocates the use of vitamins, minerals, and trace elements to improve their "physical condition" and also concludes that "their capacity noticeably increases." Similarly, he uses sociocultural methods such as early marriage and "reduction of women's occupational activities following marriage" in lieu of proved methods such as prenatal diagnosis and abortion as methods of decreasing the incidence of Down's syndrome. As a matter of fact, nowhere in his book does he mention amniocentesis as an option for parents of youngsters with Down's syndrome or for prospective mothers over the age of 35 years.

The book focuses on the uniqueness of the youngster with Down's syndrome and uses the term "so being," which is a translation from the "so seine" of Gestalt psychology. This use of this term is supposed to reflect the inherent qualities of the individual. Although Dr Wunderlich makes a strong case for the fact that persons with Down's syndrome should be treated as individuals, his "so being" concept for all youngsters with Down's syndrome imparts a homogeneity to this population that makes them a syndrome first and individual children second. I am unwilling to accept the almost species difference that he implies. The fact that children with Down's syndrome have a lower incidence of behavioral difficulties than other retarded children may be more a reflection of the early recognition of their disability with the formulation of realistic goals rather than the uniqueness of the syndrome itself.

The strength of the book lies in the author's description of the pathogenesis of Down's syndrome, the interaction of the physician with the family, and the overall educational needs of these youngsters. The date of publication of the book did not permit the recently described chromosomal contribution of the father in 21% of the cases of Down's syndrome.[1] I agree with his emphasis that the primary care physician is the only professional in a position to provide continuous and coordinated care for developmentally disabled children. Those persons who are opposed to the use of the medical model for the care of the developmentally disabled child will take strong issue with this position. The reality is that children with chronic disabilities are not a 180-day/year, five-day/week responsibility that can be resolved in community agencies and educational systems alone. The facts are that the primary care physician is still the entry point into the service system, that many developmentally disabled youngsters have medical problems, and that the physician is the person who should be available on an unlimited, continuous time basis. The physician, as Dr Wunderlich suggests, must, however, be knowledgeable, empathetic, and willing to give the time necessary to serve a population that have complex, ongoing needs. It is unfortunate that the service model he represents is diluted by his strong disease orientation toward Down's syndrome. He treats both the youngster and the family as patients and does not sufficiently emphasize the role of parents in helping to establish habilitative goals for the child.

Dr Wunderlich's book is of interest to those of us who work with children with developmental disabilities, but it falls short in many areas. The author's lack of compliance to an international effort to change the name of the syndrome from mongolism to Down's syndrome really serves no useful purpose. Unless a great deal has been lost in the translation from German to English, the complex medical and psychological concepts and terms that are presented make it very difficult to accomplish the task of having the book understandable by both laymen and professionals alike. My first choice for a text that bridges the gap between the professional and the laymen still is Smith and Wilson's book, *The Child With Down's Syndrome.*[2] This simple but comprehensive monograph can be recommended to both professionals and laymen without the many strong reservations I have about Dr Wunderlich's book.

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Principles of Pediatrics: Health Care For the Young, by Robert A. Hoekelman, S. Blatman, and P. A. Brunell, et al, $39.95, 2,025 pp, with 300 + illus, New York, McGraw-Hill Book Co Inc, 1978.

How does one review a 2,000-page textbook with five editors and 207 authors? One reviewer read completely through the reviewed text and through five other contemporary texts.[1] His comparisons were far more valid than mine can be. For what I did was to read the introduction, the general introductory chapters, some chapters authored by each of the editors, and chapters on a dozen or so clinical subjects in which I fancy myself to be somewhat of an expert. I then compared these with similar chapters in other standard textbooks.

How can one be unbiased in such a review, when many of the editors and authors are friends and colleagues? I cannot and I admit that I start out with a bias in favor of its success. Given these limitations, let me try to tell you what the editors have attempted to accomplish and how well I think they have succeeded.

The editors state that they have attempted to provide a textbook that differs from traditional textbooks in several ways. They aim at all primary care provider-pediatricians, family physicians, nurse practitioners, and physician's assistants. They attempt to provide all the information that such practitioners need to understand and to manage the health and illness of children and youth in primary care, to emphasize the maintenance of health as well as the treatment of illness, to limit the depth of discussion of illness to that needed for primary care. They try to provide understanding of all of the multiple determinants of health and illness—the environment, the psychosocial influences of family, school and community, the medical care system—in addition to

the pathophysiology of disease.

How well have they succeeded? Very unevenly, to my point of view. First the good news. They have included a great deal of information on the medical care system and how it impinges on children. Topics, such as patient compliance with physicians' recommendations, neglected in most texts, are thoroughly discussed. Current patterns of mortality, morbidity, and disability receive much more attention than usual. The limitations of medical care in determining child health are described. The family, the school, and the community are formally recognized in special chapters and sections. Whereas much of the writing on these topics is discursive and philosophic, their inclusion does set the role of the medical provider in a more realistic context.

Far more attention is paid to psychosocial problems than is common in pediatric texts. Topics such as rape, incest, and child abuse receive discussions, as well as the common behavior problems. The writing in these sections is usually sensible and unpretentious, but too often lacking in the specific details necessary for the management of such problems in the office setting.

More space is devoted to health maintenance than in other texts, but much of the added space is devoted to long-winded discussion rather than to specific information that can contribute to greater understanding or to more effective practice.

To my mind, a text must have several attributes if it is to achieve the editors' aim of providing the understanding and practical information necessary for primary health care. It must provide instruction on all of the situations likely to be encountered in primary care practice. It must clearly delineate the commonplace from the unusual, provide full guidance on the management and understanding of the commonplace, state clearly how to differentiate the unusual, and describe how and when the unusual should be referred to others.

This book does include material on physical examination, pediatric procedures, and first aid that are usually omitted from other textbooks. However, the chapters devoted to specific diseases, disturbances, or problems seldom focus in the issues emphasized by the editors: recognition, primary management, referral, and elucidation of controversial issues. Instead, they often emphasize pathophysiology, etiology, and the author's own specific approach to management. There is an elegant, up-to-date discussion of immune mechanisms, but no reference to hay fever in the "Index," no description of how to recognize or differentiate hay fever, and only the most general discussion of its management. The sections on bowlegs, knock-knees, and toeing-in give no criteria for the limits of normal, for referral, or for treatment. A 70-page chapter on diseases of the heart and blood vessels includes only a few paragraphs on recognition buried in detailed descriptions of anatomic, roentgenographic, and ECG findings.

Discussions of etiology and pathogenesis may be long, detailed, and inclusive or entirely absent, but in either case, though notable exceptions are present, they are not often closely matched to what is necessary to recognize illness or to understand controversies regarding cause or management.

The balance in emphasis between common and uncommon conditions seems to be as capricious in this as in other textbooks. Immune deficiency diseases, certainly rare, occupy 18 pages, preceded by an equally long treatise on theory. Herpes gingivostomatitis, which affects 10% to 20% of all children, gets a few paragraphs. Over 130 pages are devoted to dermatologic problems, perhaps consistent with their frequency in practice. But, within the chapter, emphasis bears little relationship to frequency, and differential diagnosis and treatment are often dealt with far too briefly. The topics of minimal brain dysfunction and hyperactive behavior get just less than three pages, most of it sensible, but hardly sufficient preparation to deal with the strongly held opinions of colleagues or parents.

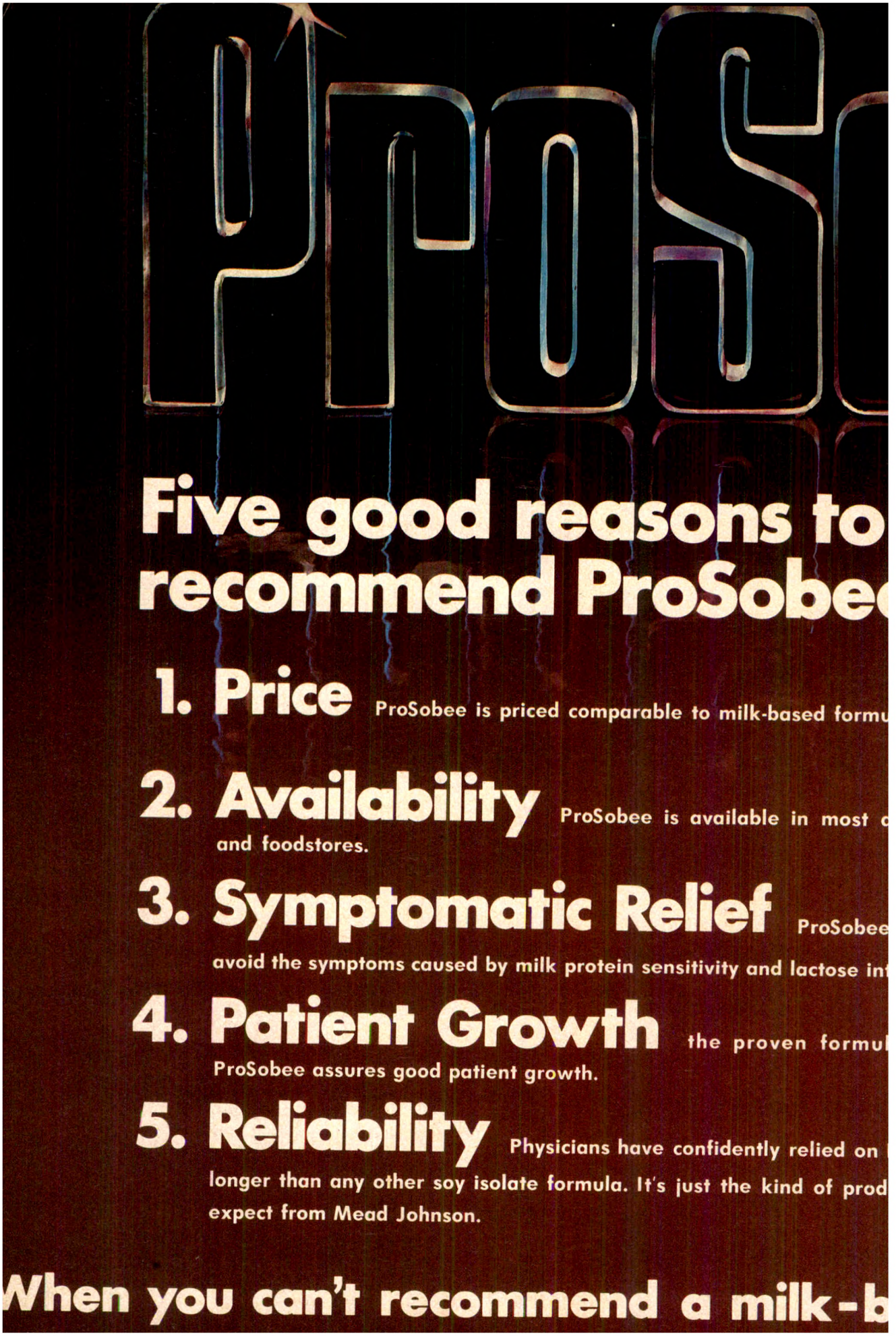
The reader should remember that most of these criticisms pertain equally to all multiauthored texts and specifically to the two other major American ones on pediatrics. I only point out that they have not been avoided in this book, which tried to be different.

I agree wholeheartedly with the editors that a new kind of text is needed, one that addresses itself to primary pediatric care. If, as I contend, this book is not the answer to this need, what kind of a book would be? I would suggest that it contain the following: (1) A detailed schedule and instructions for primary preventive services. (2) A schedule and detailed description of age-specific screening evaluations (interview, examination, and tests) with clear delineations of what variations are normal and which ones should trigger further evaluation. (3) Instructions regarding the further evaluation, interpretation, and management of abnormal findings (whether noted at screening or illness evaluations), including clinical algorithms for diagnostic, management, and referral decisions. Sufficient detail and background would be provided for complete management of common problems, for dealing with controversies raised by parents and colleagues, and for detection, emergency treatment, and referral of unusual or complicated problems. Other background information and details of the diagnosis and management of conditions for which specialist referral is usually necessary would be cited in annotated references. (4) Practical instruction in the basic skill areas of the provider: diagnostic and therapeutic procedures, interviewing, testing, counseling (including behavior modification and parent education), and self-monitoring and self-evaluation. (5) Sufficient information about the skills and approaches of professional colleagues (subspecialists, social workers, physical therapists, audiologists, speech therapists, etc) so that the primary care provider can be an informed "consumer" of their services. Until such a book is produced, this text by Hoekelman et al, is probably the closest approximation available.

This is a book worth owning, primarily because of its virtues as a pediatric textbook and only secondarily because of its attempts to be nontraditional. It does contain topics not included in many texts. It does contain more material on behavioral pediatrics and on the organization of child health care than do other texts. Some of its chapters are, indeed, concise formulations of what the primary care provider must understand and do. But to most readers, its similarities to the texts currently edited by Vaughan and by Rudolf will be more impressive than its differences. *Principles of Pediatrics* is a welcome addition to the ranks of pediatric textbooks.

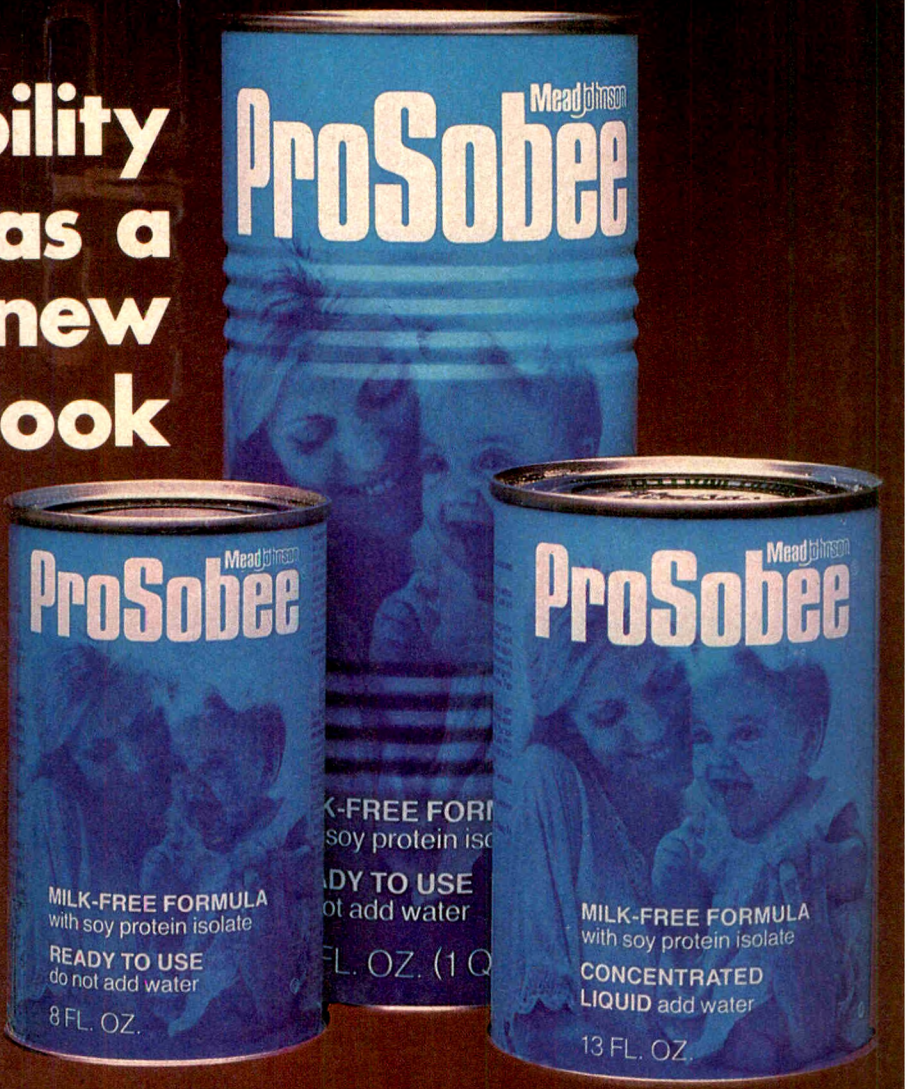
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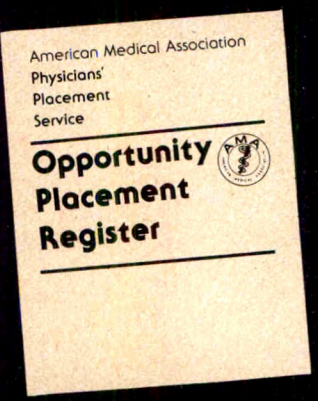
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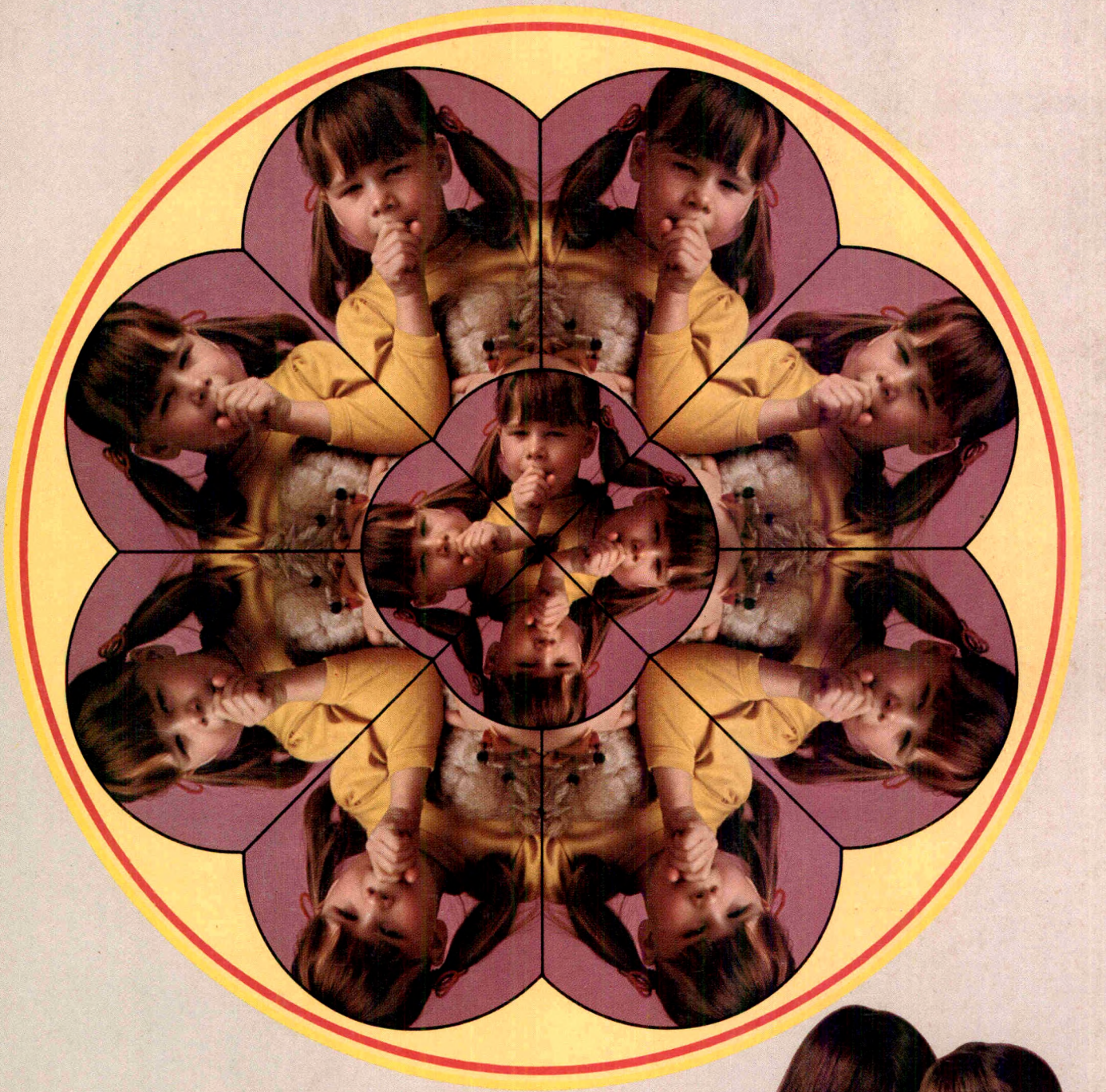
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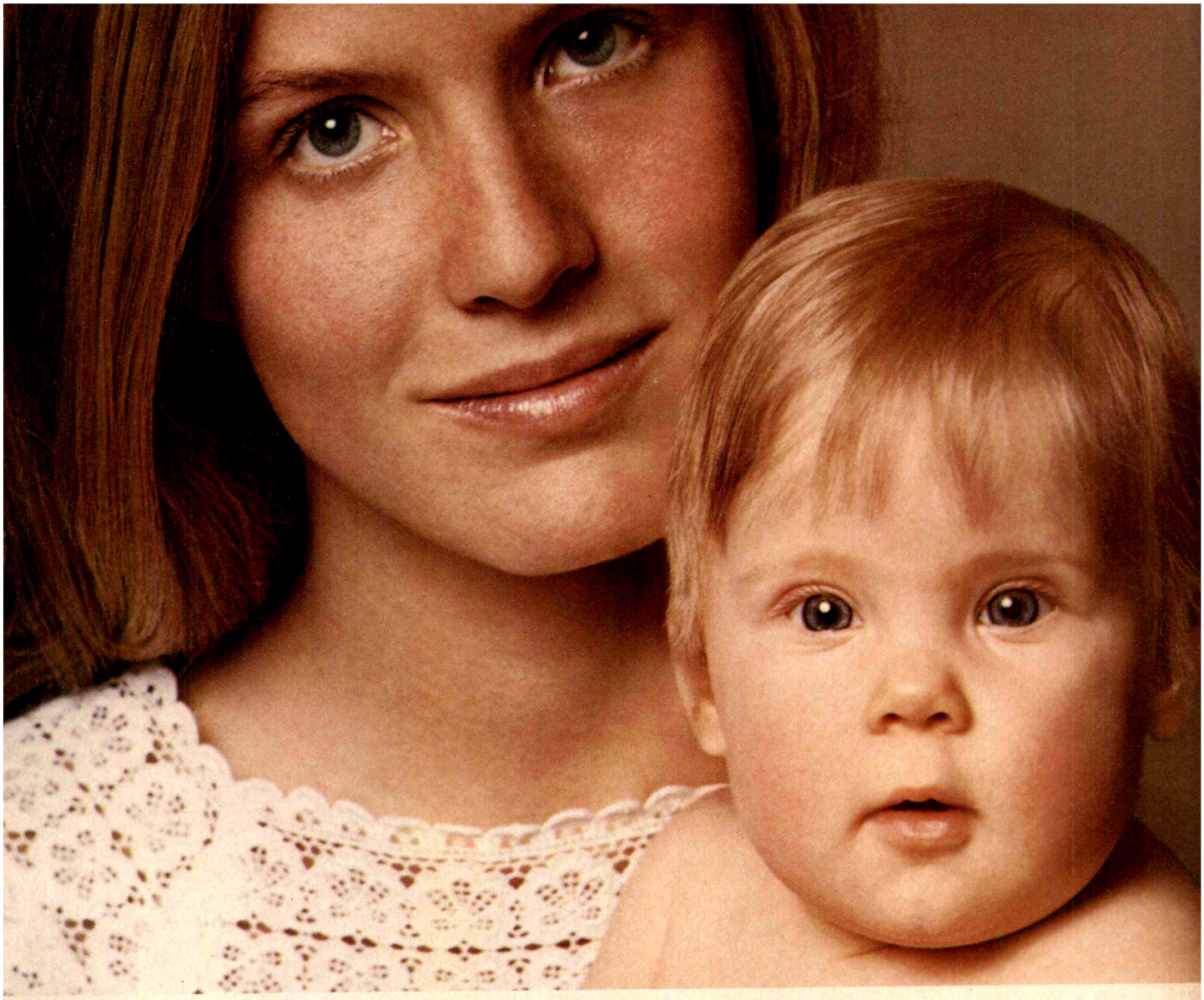
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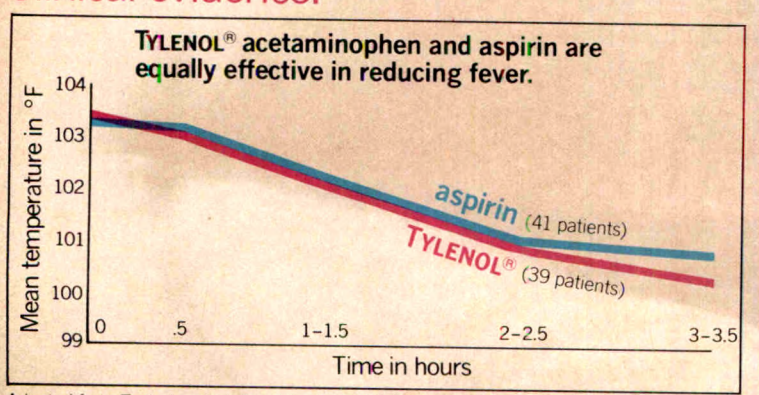
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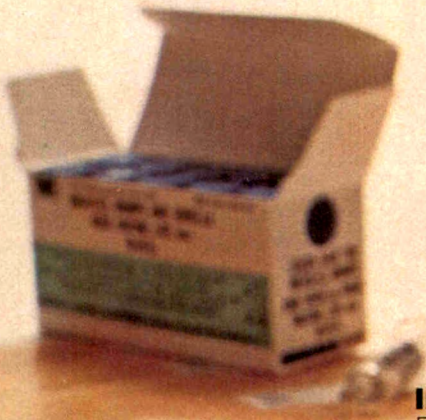
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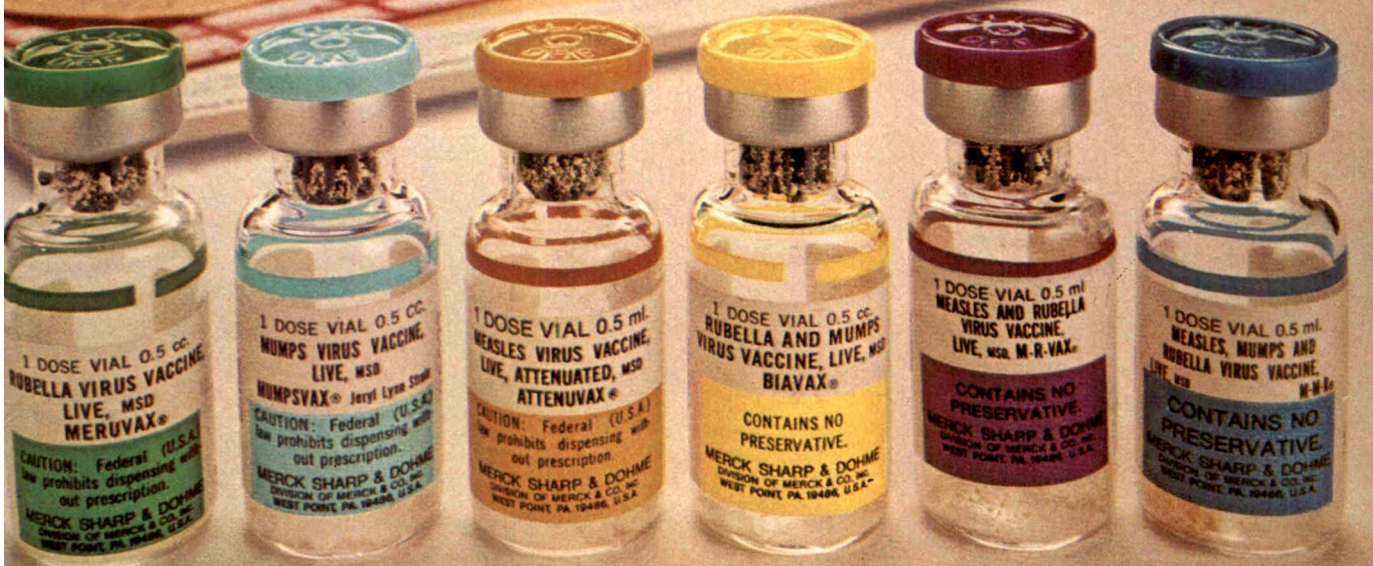
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MUMPSVAX® (Mumps Virus Vaccine, Live, MSD)—Immunization against mumps for children 15 months of age or older and adults. May be given as early as 12 months if that offers greater convenience in scheduling.

Contraindications: Pregnancy or the possibility of pregnancy within three months following vaccination (see special considerations for ATTENUVAX below); hypersensitivity to neomycin; in patients hypersensitive to chicken or chicken eggs or feathers or, for rubella-containing vaccines, duck or duck eggs or feathers, weigh benefits of immunization against potential risks of hypersensitivity reactions; any febrile respiratory illness or other active infection; for measles-containing vaccines, active untreated tuberculosis; therapy with ACTH, corticosteroids (except as replacement therapy, e.g., for Addison's disease), irradiation, alkylating agents, or antimetabolites; blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems; primary immunodeficiency states, including cellular immune deficiencies, hypogammaglobulinemic, and dysgammaglobulinemic states.

ATTENUVAX—PREGNANCY: The effects of ATTENUVAX on fetal development are unknown at this time. Live attenuated measles virus vaccine should not be given to persons known to be pregnant; furthermore, pregnancy should be avoided for three months following vaccination. Reports have indicated that natural measles during pregnancy enhances fetal risk. Increased rates of spontaneous abortion, stillbirth, congenital defects, and prematurity have been observed subsequent to natural measles during pregnancy. There are no adequate studies of the attenuated (vaccine) strain of measles virus in pregnancy. However, it would be prudent to assume that the vaccine strain of virus is also capable of inducing adverse fetal effects for up to three months following vaccination.

Vaccine administration to post-pubertal females entails a potential for inadvertent immunization during pregnancy. Theoretical risks involved should be weighed against the risks that measles poses to the unimmunized adolescent or adult. Advisory committees reviewing this matter have recommended vaccination of post-pubertal females who are presumed to be susceptible to measles and not known to be pregnant. If a measles exposure occurs during pregnancy, one should consider the possibility of providing temporary passive immunity through the administration of immune serum globulin (human).

Precautions: Administer subcutaneously; *do not give intravenously*. Epinephrine should be available for immediate use should an anaphylactoid reaction occur. Should not be given less than one month before or after immunization with other *live* virus vaccines, with the exception of monovalent or trivalent poliovirus vaccine, live, oral, which may be administered simultaneously. Vaccinations should be deferred for at least three months following blood or plasma transfusions or administration of more than 0.02 ml human immune serum globulin per pound of body weight. Rubella vaccine may be given in the immediate postpartum period to those nonimmune women who have received anti-Rh_0 (D) immune globulin (human) without interfering with vaccine effectiveness.

Attenuated measles, mumps, and rubella virus vaccines, live, given separately, may result in a temporary depression of tuberculin skin sensitivity; therefore, if a tuberculin test is to be done, it should be administered before or simultaneously with any of these virus vaccines.

Measles-Containing Vaccines—Due caution should be employed in children with a history of febrile convulsions, cerebral injury, or any other condition in which stress due to fever should be avoided. The physician should be alert to the temperature elevation which may occur 5 to 12 days after vaccination. The occurrence of thrombocytopenia and purpura has been extremely rare.

Rubella-Containing Vaccines—Excretion of live attenuated rubella virus from the throat has occurred in the majority of susceptible individuals administered rubella vaccine. There is no definitive evidence to indicate that such virus is contagious to susceptible persons who are in contact with vaccinated individuals. Consequently, transmission, while accepted as a theoretical possibility, has not been regarded as a significant risk.

Adverse Reactions: To date, clinical evaluation of the combination vaccines has revealed those adverse reactions expected to follow administration of the monovalent vaccines given separately.

Measles-Containing Vaccines—Occasionally, moderate fever (101-102.9 F); less commonly, high fever (above 103 F); rarely, febrile convulsions. Infrequently, rash, usually minimal without generalized distribution. Reactions at injection site. Local reactions characterized by marked swelling, redness, and vesiculation at the injection site of attenuated live measles virus vaccines have occurred in children who received killed measles vaccine previously; the combination vaccines were not given under this condition in clinical trials.

Experience from more than 80 million doses of all live measles vaccines given in the U.S. through 1975 indicates that significant central nervous system reactions such as encephalitis and encephalopathy, occurring within 30 days after vaccination, have been temporally associated with measles vaccine approximately once for every million doses. In no case has it been shown that reactions were actually caused by vaccine. The Center for Disease Control has pointed out that "a certain number of cases of encephalitis may be expected to occur in a large childhood population in a defined period of time even when no vaccines are administered." However, the data suggest the possibility that some of these cases may have been caused by measles vaccines. The risk of such serious neurological disorders following live measles virus vaccine administration remains far less than that for encephalitis and encephalopathy with natural measles (one per thousand reported cases). There have been reports of subacute sclerosing panencephalitis (SSPE) in children who did not have a history of natural measles but did receive measles vaccine. Some of these cases may have resulted from unrecognized measles in the first year of life or possibly from the measles vaccination. Based on estimated nationwide measles vaccine distribution, the association of SSPE cases to measles vaccination is about one case per million vaccine doses distributed, far less than the 5-10 cases of SSPE per million cases of natural measles.

Rubella-Containing Vaccines—Adverse reactions may include fever and rash; mild local reactions such as erythema, induration, tenderness, and regional lymphadenopathy; thrombocytopenia and purpura; allergic reactions such as urticaria; and arthritis, arthralgia, and polyneuritis.

Moderate fever (101-102.9 F) occurs occasionally, and high fever (103 F) occurs less commonly. Rash occurs infrequently and is usually minimal without generalized distribution. Encephalitis and other nervous system reactions have occurred very rarely.

Transient arthritis, arthralgia, and polyneuritis vary in frequency and severity with age and sex, being greatest in adult females and least in prepubertal children. Symptoms relating to joints (pain, swelling, stiffness, etc.) and to peripheral nerves (pain, numbness, tingling, etc.) occurring within approximately two months after vaccination should be considered as possibly vaccine related. These symptoms need not be associated with other features of rubella, such as fever, rash, and lymphadenopathy. In prepubertal children, the symptoms have generally been mild and of no more than three days' duration, with an incidence of less than 1 percent for reactions that would interfere with normal activity or necessitate medical attention. In teen-age girls, the rates of reactions are somewhat higher but probably do not exceed 5 to 10 percent. In women, the rates are greater and may exceed 30 percent; the symptoms in older females tend to be more prominent and of longer duration, rarely persisting for a matter of months, but have not generally interfered with normal activity. There is, at present, no evidence that the joint involvement or neuritis accompanying infection with either natural rubella or the attenuated viruses predisposes to any of the known chronic arthritic or neurologic diseases. Transient arthralgia and arthritis in nonimmune males may occur; however, as in the natural disease, the incidence is expected to be lower than in women.

Mumps-Containing Vaccines—Parotitis. Rarely, purpura and allergic reactions such as urticaria. Very rarely, encephalitis and other nervous system reactions. With the monovalent mumps vaccine, mild fever occurs occasionally, and fever above 103 F is uncommon.

Shipment, Storage, and Reconstitution: During shipment, to insure that there is no loss of potency, the vaccine must be maintained at a temperature of 10 C (50 F) or less. Before reconstitution, store vaccines at 2-8 C (35.6-46.4 F) and *protect from light*. Use only diluent supplied to reconstitute vaccines. If not used immediately, store reconstituted vaccines in a dark place at 2-8 C (35.6-46.4 F), and discard if not used within eight hours.

Color change: The usual color of the vaccine when reconstituted is pinkish to red due to the presence of phenol red, a pH indicator. Some vaccine which has been shipped in dry ice may exhibit a variation in color when reconstituted because carbon dioxide has been absorbed from the dry ice. This vaccine, if crystal clear on reconstitution, is acceptable for use whether it is red, pink, or yellow.

How Supplied: *ATTENUVAX® (Measles Virus Vaccine, Live, Attenuated, MSD)*—Single-dose vials of lyophilized vaccine, containing when reconstituted not less than 1,000 $TCID_{50}$ (tissue culture infectious doses) of measles virus vaccine expressed in terms of the assigned titer of the FDA Reference Measles Virus, and approximately 25 mcg neomycin.

BIAVAX® (Rubella and Mumps Virus Vaccine, Live, MSD)—Single-dose vials of lyophilized vaccine, containing when reconstituted not less than 1,000 $TCID_{50}$ of rubella virus vaccine, live, and 5,000 $TCID_{50}$ of mumps virus vaccine, live, expressed in terms of the assigned titer of the FDA Reference Rubella and Mumps Viruses, and approximately 25 mcg neomycin.

MERUVAX® (Rubella Virus Vaccine, Live, MSD)—Single-dose vials of lyophilized vaccine, containing when reconstituted not less than 1,000 $TCID_{50}$ of rubella virus vaccine expressed in terms of the assigned titer of the FDA Reference Rubella Virus, and approximately 25 mcg neomycin.

M·M·R® (Measles, Mumps and Rubella Virus Vaccine, Live, MSD)—Single-dose vials of lyophilized vaccine, containing when reconstituted not less than 1,000 $TCID_{50}$ of measles virus vaccine, live, attenuated, 5,000 $TCID_{50}$ of mumps virus vaccine, live, and 1,000 $TCID_{50}$ of rubella virus vaccine, live, expressed in terms of the assigned titer of the FDA Reference Measles, Mumps, and Rubella Viruses, and approximately 25 mcg neomycin.

M·R·VAX® (Measles and Rubella Virus Vaccine, Live, MSD)—Single-dose vials of lyophilized vaccine, containing when reconstituted not less than 1,000 $TCID_{50}$ of measles virus vaccine, live, attenuated, and 1,000 $TCID_{50}$ of rubella virus vaccine, live, expressed in terms of the assigned titer of the FDA Reference Measles and Rubella Viruses, and approximately 25 mcg neomycin.

MUMPSVAX® (Mumps Virus Vaccine, Live, MSD)—Single-dose vials of lyophilized vaccine, containing when reconstituted not less than 5,000 $TCID_{50}$ of mumps virus vaccine expressed in terms of the assigned titer of the FDA Reference Mumps Virus, and approximately 25 mcg neomycin.

Each of these vaccines is supplied as a single-dose vial packed with a disposable syringe containing diluent and fitted with a 25-gauge, 5/8" needle, and as a box of 10 single-dose vials with an accompanying box of 10 diluent-containing disposable syringes with affixed needles.

For more detailed information, consult your MSD representative or see full prescribing information.
Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486. J6VA02R3

MSD
MERCK SHARP & DOHME

Because we don't take quality for granted,

you can.



700648

V-Cillin K®

Lilly

penicillin V potassium

the most widely prescribed brand of oral penicillin

Tablets—125, 250, and 500 mg.* Oral Solution—125 and 250 mg.*/5 ml.

V-CILLIN K®
penicillin V potassium

Brief Summary. Consult the package literature for prescribing information.

Description: V-Cillin K is the potassium salt of penicillin V. This chemically improved form combines acid stability with immediate solubility and rapid absorption.

Indications: For the treatment of mild to moderately severe pneumococcal respiratory tract infections and mild staphylococcal skin and soft-tissue infections that are sensitive to penicillin G. See the package literature for other indications.

Contraindication: Previous hypersensitivity to penicillin.

Warnings: Serious, occasionally fatal, anaphylactoid reactions have been reported. Some patients with penicillin hypersensitivity have had severe reactions to a cephalosporin; inquire about penicillin, cephalosporin, or other allergies before treatment. If an allergic reaction occurs, discontinue the drug and treat with the usual agents (e.g., epinephrine or other pressor amines, antihistamines, or corticosteroids).

Precautions: Use with caution in individuals with histories of significant allergies and/or asthma. Do not rely on oral administration in patients with severe illness, nausea, vomiting, gastric dilatation, cardiospasm, or intestinal hypermotility. Occasional patients will not absorb therapeutic amounts given orally. In streptococcal infections, treat until the organism is eliminated (minimum of ten days). With prolonged use, nonsusceptible organisms, including fungi, may overgrow; treat superinfection appropriately.

Adverse Reactions: Hypersensitivity, including fatal anaphylaxis. Nausea, vomiting, epigastric distress, diarrhea, and black, hairy tongue. Skin eruptions, urticaria, reactions resembling serum sickness (including chills, edema, arthralgia, prostration), laryngeal edema, fever, and eosinophilia. Infrequent hemolytic anemia, leukopenia, thrombocytopenia, neuropathy, and nephropathy, usually with high doses of parenteral penicillin. [102175]

*Equivalent to penicillin V.

Additional information available to the profession on request.

Eli Lilly and Company
Indianapolis, Indiana 46206


"WHO COUGHED?"



When unproductive coughs startle,

HYCOTUSS® Expectorant provides effective antitussive/expectorant action — controls coughing for up to 6 hours and helps liquefy bronchial secretions to aid expectoration.

HYCOTUSS® EXPECTORANT C III

Each teaspoonful (5 ml) contains 5 mg hydrocodone bitartrate (WARNING: May be habit forming), 100 mg guaifenesin and alcohol U.S.P. 10% v/v

Cough relief for children under 12

USUAL DOSAGE: *Children under 2 years* – calculate as hydrocodone, 0.3 mg/kg/24 hours, divided into 4 equal doses. *Children 2 to 12 years* – ½ teaspoonful after meals and at bedtime, not less than 4 hours apart. *Children over 12 and adults* – 1 teaspoonful after meals and at bedtime, not less than 4 hours apart.

Please see brief summary of prescribing information below.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

CONTRAINDICATIONS: HYCOTUSS Expectorant should not be used in patients with hypersensitivity to hydrocodone or guaifenesin.

WARNINGS: HYCOTUSS Expectorant should be prescribed and administered with the same degree of caution appropriate for the use of other oral narcotic-containing medications since it can produce drug dependence and, therefore, has the potential for abuse. Patients should be warned not to drive a car or operate machinery if they become drowsy or show impaired mental and/or physical abilities while taking HYCOTUSS Expectorant. Patients receiving narcotic analgesics, phenothiazines, other tranquilizers, sedative-hypnotics or other central nervous system depressants (including alcohol) concomitantly with HYCOTUSS Expectorant may exhibit an additive central nervous system depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

PRECAUTIONS: Before prescribing medication to suppress or modify cough, it is important to ascertain that the underlying cause of cough is identified, that modification of cough does not increase the risk of clinical or physiologic complications, and that appropriate therapy for the primary disease is provided.

ADVERSE REACTIONS: Adverse reactions, when they occur, include sedation, nausea, vomiting and constipation.

DRUG INTERACTIONS: The central nervous system depressant effects of HYCOTUSS Expectorant may be additive with that of other central nervous system depressants. See WARNINGS. 6072-3

Oral prescription where permitted by State law.

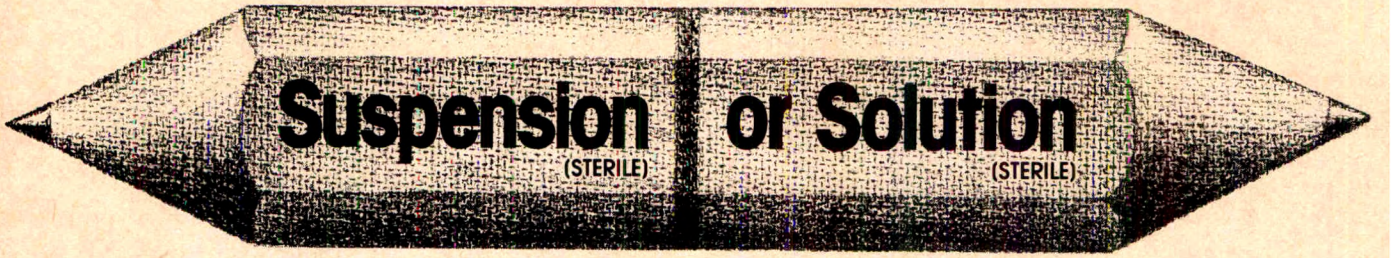
HYCOTUSS® is an Endo registered U.S. trademark 6070-2BS

Endo Laboratories, Inc.
Subsidiary of the DuPont Company
Garden City, New York 11530

DUPONT

Please don't just Rx "Cortisporin® Otic"...Specify:

(polymyxin B-neomycin-hydrocortisone)



INDICATIONS:
For the treatment of superficial bacterial infections of the external auditory canal caused by organisms susceptible to the action of the antibiotics, and for the treatment of infections of mastoidectomy and fenestration cavities caused by organisms susceptible to the antibiotics.

DESCRIPTION:
Each cc contains: Aerosporin® brand
Polymyxin B Sulfate ..... 10,000 units
Neomycin Sulfate ..... 5 mg
(equivalent to 3.5 mg neomycin base)
Hydrocortisone ..... 10 mg (1%)
The vehicle contains the inactive ingredients cetyl alcohol, propylene glycol, polysorbate 80, purified water and thimerosal (preservative) 0.01%.

PRECAUTIONS:
This drug should be used with care in cases of perforated eardrum and in long-standing cases of chronic otitis media because of the possibility of ototoxicity caused by neomycin.

ADVERSE REACTIONS:
Neomycin is a not uncommon cutaneous sensitizer. There are articles in the current literature that indicate an increase in the prevalence of persons sensitive to neomycin.

BENEFITS:
Indications include infections of mastoidectomy and fenestration cavities caused by organisms susceptible to the antibiotics.

INDICATIONS:
For the treatment of superficial bacterial infections of the external auditory canal caused by organisms susceptible to the action of the antibiotics.

DESCRIPTION:
Each cc contains: Aerosporin® brand
Polymyxin B Sulfate ..... 10,000 units
Neomycin Sulfate ..... 5 mg
(equivalent to 3.5 mg neomycin base)
Hydrocortisone ..... 10 mg (1%)
The vehicle contains the inactive ingredients glycerin, hydrochloric acid, propylene glycol, purified water and potassium metabisulfite (preservative) 0.1%.

PRECAUTIONS:
This drug should be used with care when the integrity of the tympanic membrane is in question because of the possibility of ototoxicity caused by neomycin.

ADVERSE REACTIONS:
Neomycin is a not uncommon cutaneous sensitizer. There are articles in the current literature that indicate an increase in the prevalence of persons sensitive to neomycin. Stinging and burning have been reported when this drug has gained access to the middle ear.

BENEFITS:
Clear visualization of field. Does not have to be shaken.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS COMMON TO BOTH PRODUCTS:

CONTRAINDICATIONS:
In individuals who have shown hypersensitivity to any of the components, and in herpes simplex, vaccinia, and varicella.
WARNINGS:
Prolonged treatment may result in overgrowth of non-susceptible organisms and fungi. If the infection is not improved after one week, cultures and susceptibility tests should be repeated to verify the identity of the organism, and to determine whether therapy should be changed.
When using neomycin-containing products to control secondary infection in the chronic dermatoses, such as otitis externa, it should be borne in mind that the skin in these conditions is more liable than is normal skin to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling, and itching; it may be manifest simply as a failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.
PRECAUTIONS:
If sensitization or irritation occurs, medication should be discontinued promptly. Patients who prefer to warm the medication before using should be cautioned against heating the solution above body temperature, in order to avoid loss of potency.
Treatment should not be continued for longer than ten days. Allergic cross-reactions may occur which could prevent the use of any or all of the following antibiotics for the treatment of future infections: kanamycin, paromomycin, streptomycin, and possibly gentamicin.
HOW SUPPLIED:
Both products available in 10 cc bottles with sterile droppers.

Both products offer you:

- Wide range of antibacterial activity, including action against many strains of *Pseudomonas aeruginosa* and *Proteus*.
- Direct anti-inflammatory action, relieving associated itching, swelling and pain.
- Economy for your patients.

Wellcome / **Burroughs Wellcome Co.**
Research Triangle Park
North Carolina 27709



For allergic dermatoses
with strong emotional overlay

Atarax®
(hydroxyzine HCl)

Tablets: 10 mg, 25 mg, 50 mg, and 100 mg
Syrup: 10 mg per 5 ml, ethyl alcohol 0.5% v/v

As adjunctive therapy

- rapid antianxiety action
- demonstrated antihistaminic/antipruritic activity

Contraindications: Hypersensitivity to hydroxyzine. Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit, induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Clinical data in human beings are inadequate to establish safety in early pregnancy. Until such data are available, hydroxyzine is contraindicated in early pregnancy.

Precautions: Hydroxyzine may potentiate the action of central nervous system depressants such as meperidine and barbiturates. In conjunctive use, dosage for these drugs should be reduced. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery.

Adverse Reactions: Drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon dosage reduction. Dryness of the mouth may occur with higher doses. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.

Supply: Tablets, containing 10 mg hydroxyzine hydrochloride, 100's and 500's; Tablets, containing 25 mg or 50 mg, 100's, 500's, and Unit Dose (10 x 10's); Tablets, containing 100 mg, 100's and Unit Dose (10 x 10's); Syrup, containing 10 mg per teaspoonful (5 ml) and ethyl alcohol 0.5% v/v, pint bottles.

Before prescribing or administering, see package circular.

ROERIG Pfizer
A division of Pfizer Pharmaceuticals
New York, New York 10017

Expand Your Horizons And Those of Your Nursing Home Patients



This compilation of articles and memoranda is geared to further your understanding of your role in regard to: your nursing home patients; their families; and the nursing home staff. Published by the American Medical Association, **The Medical Director in the Long-Term Care Facility** is the only book of its kind.

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The Medical Director in the Long-Term Care Facility should help you to meet the nursing home problems which you encounter. Use the coupon to order this valuable compendium today.

$3.50

S/J

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American Medical Association
535 N. Dearborn/Chicago, IL 60610

Please send _____ copy(ies) of THE MEDICAL DIRECTOR IN THE LONG-TERM CARE FACILITY, OP-22, at $3.50 each. Enclosed is $_____, payable to the AMA.

Name _____

Address _____

City/State/Zip _____

ACCURBRON™
theophylline

DESCRIPTION: Each ml contains anhydrous theophylline 10 mg (50 mg per 5 ml teaspoonful) and alcohol 7.5% in a pleasant tasting vehicle.

ACTIONS: Theophylline, 1, 3-dimethylxanthine, is a bronchodilator. It is rapidly absorbed when given as an elixir. It acts by inhibiting the enzyme phosphodiesterase which degrades cyclic AMP. Its plasma half-life (T ½) varies widely because of differences in the rate of metabolism.

Theophylline relaxes the smooth muscle of the respiratory tract and relieves bronchospasm. Its bronchodilator effect is minimal in the absence of bronchospasm.

Other actions of theophylline include dilation of pulmonary, coronary and renal arteries and increased cardiac output, and CNS stimulation. Usual doses increase blood pressure only slightly. Theophylline also has a mild diuretic action.

INDICATIONS: For the relief of bronchial asthma (acute or chronic) and reversible bronchospasm associated with obstructive pulmonary diseases such as chronic bronchitis and emphysema.

Theophylline relieves the shortness of breath, wheezing and dyspnea associated with asthma and improves pulmonary function (increases flow rates and vital capacity). In doses sufficient to produce therapeutic serum concentrations (10-20 μg/ml), theophylline would also prevent the symptoms of chronic asthma and suppress exercise-induced asthma. It is especially useful for long-term treatment of bronchospasm because tolerance to the bronchodilator effect of theophylline rarely occurs.

Corticosteroids may be given in conjunction with theophylline, if needed.

CONTRAINDICATIONS: Patients with peptic ulcers, active gastritis, and hypersensitivity or idiosyncrasy to theophylline and other methylxanthines.

WARNINGS: Should not be given concomitantly with other xanthine-containing drugs because of the potential for serious toxicity from elevated xanthine serum levels. Also, liquids containing xanthines (tea, coffee, etc.) should be avoided.

Use in Pregnancy: Safety for use during pregnancy has not been established. Theophylline is excreted in the milk. Use during lactation and in women of childbearing potential requires that benefits be weighed against possible hazards to fetus or child.

PRECAUTIONS: As with all theophylline-containing products, use with caution in patients with cardiovascular disease, in infants and the elderly, and in patients with liver, kidney and heart disease.

ADVERSE REACTIONS: **Gastrointestinal:** loss of appetite, nausea, vomiting, gastric irritation. **CNS:** irritability, especially in children, insomnia, headache, dizziness, convulsions. These side-effects are usually associated with high theophylline serum levels (exceeding 20 μg/ml). **Cardiovascular:** palpitations, sinus tachycardia and increased pulse rate, usually mild and transient.

Other side-effects may include increased irritation with dehydration, muscle twitching and increased SGOT levels.

DRUG INTERACTIONS: Theophylline increases the excretion of lithium carbonate and may enhance the sensitivity and toxicity of digitalis derivatives and sympathomimetic amines. Doses higher than usual may increase the effect of oral anticoagulants. Concomitant use with erythromycin, clindamycin, lincomycin and troleandomycin may increase theophylline serum levels.

Colorimetric methods for serum uric acid are affected by theophylline. Spectrophotometric methods of theophylline in serum are affected by furosemide, sulfathiazole, phenylbutazone, probenecid and theobromine.

DOSAGE AND ADMINISTRATION: Dosage must be individualized. Accepted therapeutic serum levels for theophylline are 10-20 μg/ml. Its metabolism may vary greatly with age, among individuals and in patients with liver, kidney and heart disease. Metabolism may be stable within the same individual. However, careful monitoring for manifestations of toxicity and periodic determinations of theophylline serum levels are necessary, especially for prolonged therapy and with high doses.

Children: The following table may be used with the graduated measuring spoon for Accurbron:

ACCURBRON™ (theophylline) — PEDIATRIC DOSAGE CALCULATION TABLE

Starting dosage[1]: (All ages for first 3 days[2]) — **4 mg/kg body wt every 6 hours not to exceed 100 mg (10 ml Accurbron)**

Age	Body Weight		Dose/6 hours				
	lbs	kgs	3 mg/kg	4 mg/kg	5 mg/kg	6 mg/kg	7 mg/kg
Under 9 years*	10	4.5	1 ml	2 ml	2 ml	3 ml	3 ml
average dose	20	9	3 ml	4 ml	5 ml	5 ml	6 ml
4-6 mg/kg/6 hrs.[1]	30	14	4 ml	6 ml	7 ml	8 ml	10 ml
	40	18	5 ml	7 ml	9 ml	11 ml	13 ml
	50	23	7 ml	9 ml	12 ml	14 ml	16 ml
	60	27	8 ml	11 ml	14 ml	16 ml	19 ml
	70	32	10 ml	13 ml	16 ml	19 ml	22 ml
9-12 years*	80	36	11 ml	14 ml	18 ml	22 ml	25 ml
average dose	90	41	12 ml	16 ml	20 ml	25 ml	29 ml
4-5 mg/kg/6 hrs.[1]	100	45	14 ml	18 ml	22 ml	27 ml	32 ml

ACCURBRON contains 10 mg theophylline (anhydrous) per ml.

1. Average dosage from: Wyatt R, Weinberger M, Hendeles L: Oral theophylline dosage for the management of chronic asthma. **J Ped 92:** 125-130,1978.
2. Mitenko PA, Ogilvie RI: Rapidly achieved plasma concentration plateaus, with observations on theophylline kinetics. **Clin Pharmacol Therap 13:** 329-335, 1972.

*Do not exceed this dosage without careful clinical monitoring or checking theophylline serum level because of the increased risk of side effects when serum levels exceed 20 μg/ml.

Adults: Recommended starting dose is 100 to 200 mg (10 to 20 ml) every 6 hours. The adequacy of the dose should be determined by clinical response and periodic monitoring of theophylline serum levels.

May be given after meals with water to minimize possible G.I. irritation.

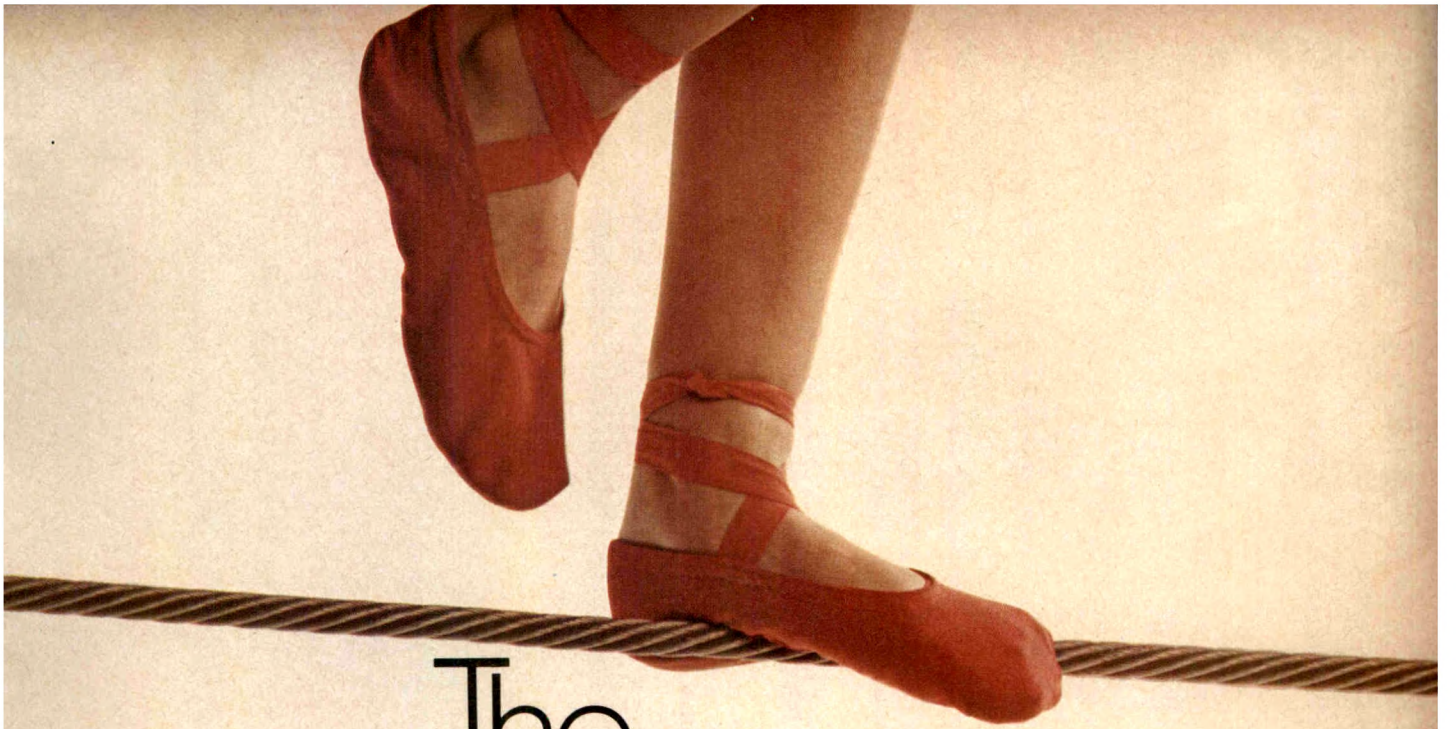
OVERDOSAGE: Theophylline has a narrow therapeutic index and toxicity is likely to occur when serum levels exceed 20 μg/ml. Usual signs of overdosage are anorexia, nausea, vomiting, irritability, headache. Gross overdosage, especially in children, may lead to seizures and death without preceding symptoms of toxicity. Treatment is symptomatic (prompt induction of emesis and gastric lavage, supportive therapy, hemodialysis, etc.).

CAUTION: Federal law prohibits dispensing without prescription.

HOW SUPPLIED: As a dye-free liquid in pint bottles (NDC 0183-5002-05) withthe graduated measuring spoon for Accurbron.

DOW

Dow Pharmaceuticals
The Dow Chemical Company
Indianapolis, Indiana 46268



The Theophylline tightrope.

Maintain the balance with Accurbron.

In theophylline therapy, the therapeutic range is narrow. Serum levels in the 10 mcg/ml to 20 mcg/ml range are necessary for optimum effect with minimal side effects. Accurbron offers an effective bronchodilator for the symptomatic relief of bronchial asthma with simplified delivery system for more accurate dosage.

For easy dosage calculation, each milliliter of Accurbron contains 10 mg. anhydrous theophylline. Then, for precise measurement, a special combination spoon and vial is calibrated to deliver the measured dose of Accurbron.*

And, with the acceptable, neutral flavor of Accurbron flavor fatigue is less likely to occur.



*A combination spoon and vial, graduated in milliliters to assure more accurate dosage, is packed with each pint bottle of Accurbron.



ACCURBRON™
theophylline

Each ml. contains anhydrous theophylline 10 mg. and alcohol 7.5%

DOW

Dow Pharmaceuticals
The Dow Chemical Company
Indianapolis, Indiana 46268

See opposite page for prescribing information



Just a touch can transfer impetigo.

And just a touch of the right antibiotic can help clear it up.

Neosporin Ointment can help control minor cases of impetigo before other children catch it from your young patient, and it may be used as an adjunct to appropriate systemic therapy in more extensive disease. Neosporin Ointment provides broad, reliable antibiotic action against susceptible organisms—notably *Staphylococcus* and *Streptococcus*— with antibiotics that are seldom used systemically.

Neosporin® Ointment

(polymyxin B—bacitracin—neomycin)

Each gram contains: Aerosporin® brand Polymyxin B Sulfate 5,000 units; zinc bacitracin 400 units; neomycin sulfate 5 mg (equivalent to 3.5 mg neomycin base); special white petrolatum qs. In tubes of 1 oz and 1/2 oz and 1/32 oz (approx.) foil packets.

Warning: Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

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Precautions: As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

Adverse Reactions: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

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Warnings: Do not administer more frequently than every 6 hours, or within 12 hours after rectal dose of any preparation containing theophylline or aminophylline. Do not give other compounds containing xanthine derivatives concurrently.

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Precautions: Use with caution in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur (frequently dose-related). During therapy, maintain adequate fluid intake and perform frequent urinalyses with careful microscopic examination and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Septra. *Blood Dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic Reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal Reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *C.N.S. Reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous Reactions:* Drug fever, chills, and toxic nephrosis with oliguria and anuria. Periarteritis nodosa and L.E. phenomenon have occurred. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia; cross-sensitivity may exist with these agents. In rats, long-term administration of sulfonamides has produced thyroid malignancies.

Dosage and Administration: Not recommended for use in infants less than two months of age.

ACUTE OTITIS MEDIA IN CHILDREN: The recommended dose for children with acute otitis media is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, given in two divided doses every 12 hours for 10 days. The following table is a guideline for the attainment of this dosage using Septra Tablets or Suspension.

Children: Two months of age or older:

Weight		Dose—every 12 hours	
lb	kg	Teaspoonfuls	Tablets
20	9	1 (5 ml)	½
40	18	2 (10 ml)	1
60	27	3 (15 ml)	1½
80	36	4 (20 ml)	2 (or 1 DS tablet)

For patients with renal impairment:

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15–30	Half of the usual dosage regimen
Below 15	Use Not Recommended

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*Clinical results do not necessarily correspond with *in vitro* data.

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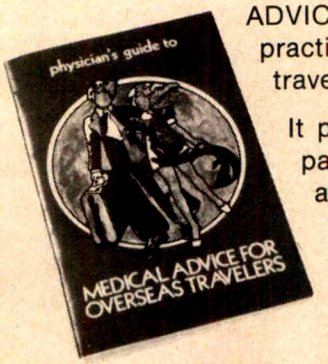
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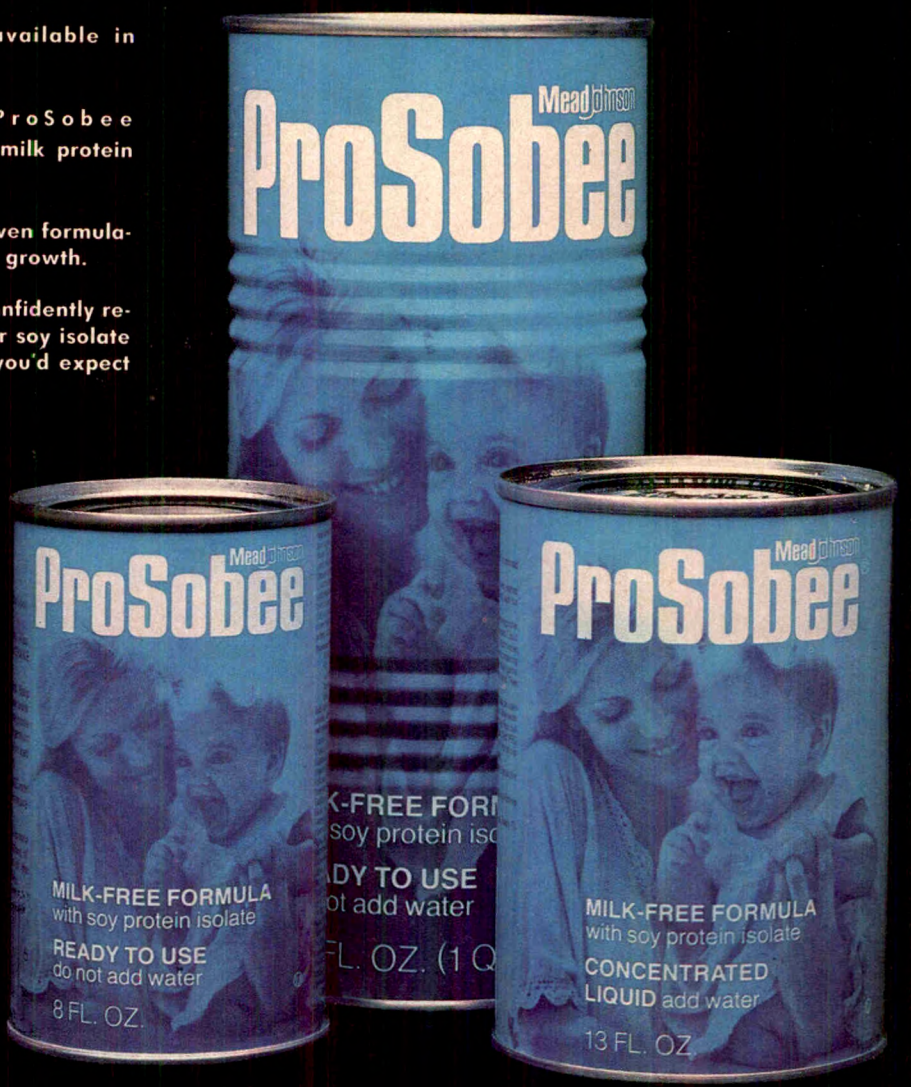
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On the Impossibility of Overriding the Influence of the Family

Firkowska and colleagues[1] at the Polish Academy of Science have written a fascinating article found in a recent issue of *Science* on the relative contribution of familial and extrafamilial factors to the mental development of children. This report points up the continuing debate among social planners, governmental officials, and academicians about what effects social policy has on the cognitive and emotional development of children. To state it differently, one can ask how effective can government-sponsored programs be in altering (hopefully remediating) the negative effects of a variety of life factors on child development.

The study is a scientific attempt to isolate variables that seem important in accounting for variations in cognitive development in schoolchildren. Warsaw was rebuilt after World War II following a social policy of equal housing and educational opportunity for all children, regardless of the social, educational, and occupational status of their parents. Consequently, families of a variety of social classes and occupations were housed side by side with the same social, educational, commercial, and medical supportive services and opportunities. In this human laboratory, the authors realized that they had a unique opportunity to partial out the effects of family variables from extrafamilial variables on the cognitive development of children, as assessed by the Raven Progressive Matrices Test, a widely used, nonverbal intelligence test. They established the following three classes of variables: (1) family (education and occupation); (2) district (how urban or suburban the area); and (3) school (an index of the "quality" of each particular elementary school).

Using multivariate statistical methods, their results indicated that the three categories of variables combined accounted for a total of 10.6% of Raven test variance ($r = .326$) and that from 85% to 97% of this covariation was attributable to family variables. Only 3.3% of the explained variance was attributable to the two extrafamilial variable classes. The authors concluded that social policy was effective in equalizing school and district variables across the population, but that such equalization was not effective in overriding other, more pronounced influences on mental performance in children.

> It is plain, nevertheless, that societal changes over a generation have failed to override forces that determine the social class distribution of mental performance among children. For further elucidation of the determinants of cognitive abilities, we need to turn our attention to intrinsic [familial] factors.[1]

This study, along with other major research enterprises,[2] has consistently pointed up the difficulty of altering a variety of deficits through programs initiated outside the home in either schools or community settings. Head Start has taught us that it requires long-term commitments and enormous resources to effect psychological and cognitive change in children. We are slowly learning that it is difficult if not impossible to override the basic influence that family life has on a host of developmental phenomena.

An interesting parallel has emerged in the area of emotional health and illness that deserves mention. For many years, mental health professionals confined their practice to the patient who came to see them and they had no regard for the influence of family members and other important persons in the patient's life. In the 1950s, several theorists and clinicians were struck by the inability of schizophrenic patients to maintain adequate functioning once hospitalization was completed, and they were often concerned about the subtle sabotage of family members in not supporting the continued recovery of the patient. These findings contributed to a shift in thinking about the nature of mental illness and led to a new field of research and treatment where the object of study was no longer the individual but the family system. The emphasis from this perspective was that a behavioral disorder cannot be treated outside of an interpersonal context.

As with research in schizophrenia, the Firkowska et al report emphasizes the difficulty in overriding the effects of family influence on cognitive development even after 30 years of enforced social policy. Varying gains in IQ as a result of specialized programs often fail to be maintained once such extrafamilial remediation and enrichment programs are terminated. As the authors suggest, schooling may actively reinforce inequalities caused by family backgrounds.[3] How, then, can society enrich child development in a meaningful way if the ever-growing body of research constantly points up the difficulty of overriding family influence? Firkowska et al[1] conclude their article by

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suggesting that "an educational policy that would improve levels of cognitive ability would require more research on the relation of parental occupation, education, and other family factors to schooling and the larger environment."

Perhaps we might extend their statement to suggest that family variables are more important in determining educational success than are "most" others and that because of this, intervention might best be focused on the family as a unit rather than on the child outside the family context. Such a development would shift the focus from an individual child to an interpersonal unit, preventing the oft-quoted tug-of-war where values of scholarship implanted at school sharply contrast with values based on survival at home. As in family treatment, then, this line of thinking would redefine the object of enrichment as the family rather than as the child alone and would open up a wealth of potential avenues for intervention. Using such an approach, one would hope such interventions would be mutually reinforcing and stimulating for all family members within several domains of family functioning.

How one might go about developing such a program is far from clear; for while the family resides at the core of procreation and subsequent physical and emotional development, it presents a series of extraordinarily complex research problems due to its multigenerational history, its ethnicity, its constant alteration in content and membership, and its mobility. Unquestionably, more research is needed in this area to identify related family variables.

Firkowska et al suggest that parental occupation and education are adequate indicators of "family microculture" and status, which are important determinants of how education and knowledge are viewed within the family. Although important in the sense of reaching a level of statistical significance, it should be kept in mind, however, that these two variables combined accounted for only 10.3% of Raven test variance. This leaves 89.7% of Raven score variation unaccounted for. So, although education and parental occupation may significantly contribute to a child's IQ and presumably to success in school, there are undoubtedly a host of other family variables that make significant contributions in this regard (L. Fisher, PhD, and J. E. Jones, PhD, unpublished data, 1978).

Perhaps too, the recent public focus on the stability of the family as a major unit of society will generate increased emphasis and public funding for continued research. We need to know a great deal more about how families function and to develop more sophisticated tools for reliably assessing various aspects of the family before we will have the skills to effectively and ethically intervene in appropriate areas of family behavior. The Firkowska et al report adds to the growing body of knowledge supporting a family focus.

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Rodney Shapiro, PhD, commented on an earlier draft of this article.

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Where Have All the Fathers Gone?

Behavior disorders, learning problems, psychosomatic complaints, and poor adaptation to chronic illness are demanding increasingly more time from today's pediatricians. The incidence and seriousness of these problems suggests serious troubles within the American family.

As a pediatric educator, I am troubled by major deficiencies in pediatric training in regard to early identification of these disorders, lack of knowledge as to effective treatment modalities, and poor utilization of supporting resources. Of especial concern, however, is the dearth of attention given to behavior and family counseling in pediatric training. Nowhere is this deficiency more apparent than in the neglect of fathers in pediatric education.

Changes in American Family Life

The American family as we know it, or at least are accustomed to think of it, appears to be under tremendous social and economic pressure. In 1976, fifty-four percent of mothers with school-age children and 37% with preschool-age children were working out-

side the home.[1] Apparently, most of these mothers must work for mere economic survival. One of every three marriages now eventually succumbs to divorce, and even more sobering is the prospect that four of every ten children born in 1970 will spend part of their childhood in a single-parent family.[2]

Parents seem more guilty, anxious, and unsure of themselves than ever and often look to their pediatrician or primary care physician for parenting guidelines. To quote from Keniston, "The discomforts and anxieties of today's parents are not nightmares dreamed up from nothing: they reflect deep changes in family life and society. Americans have not had an easy time comprehending these changes—or imagining how to deal with them—in large part because our reactions are shaped by an outmoded set of views about how families work."[3]

Inadequacies in Pediatric Training

Is today's pediatrician in tune with how families work? Pediatric house officers learn to recognize and perhaps treat every disease imaginable, even though the opportunity to manage many of these biomedical problems in practice is remote. Contrast this situation with the dearth of attention given in pediatric education to the dynamics of family interaction and parenting, even though the opportunity to intervene when parenting is ineffective is highly probable and necessary, especially when one considers that pediatrics as a specialty is recognized as being highly preventative and educative in philosophy.

Where there are attempts to keep pediatricians informed and knowledgeable about parenting disorders, one wonders how "outmoded" this information might be. For example, there is a complete void in the pediatric literature and pediatric postgraduate education on the present role and status of fathers within American family life. Since the role of the pediatrician, in addition to providing high-quality medical care, is also to provide educational services to parents in order to help children achieve their full developmental potential, then why has there been such neglect in pediatric education of the father's impact on his children?

The Absent Father

Mothers are ever more frequently calling attention to the dilemma of the physically and/or emotionally absent father. This complaint by mothers is often articulated when the child is brought to the pediatrician because of problems in behavior, learning, or adaptation to chronic illness. Whether there is a direct cause-and-effect relationship between the symptom and the father's absence is often not clear, but what has become clear is that cure or significant relief of the problem requires the active participation of the father or some significant male model for the child.

Although the participation of the father is a necessary ingredient in effective therapy of behaviorally disordered children and in the realization of potential for the chronically handicapped, obtaining the active participation of father can be a major obstacle. Many fathers have "tuned out" their children and many children have "tuned out" their fathers. It is tempting to lay blame on these fathers; however, many of these fathers feel weakened and ineffective because of external forces working on the family. Keniston has suggested, "Parents are not abdicating—they are being dethroned." This seems particularly true for fathers.

These thoughts call to mind a popular song of the 1960s with the refrain, "Where have all the flowers gone?" echoing the younger generation's sadness and discontent with what they believed to be an immoral war. Many of the present younger generation might legitimately ask, "Where have all our fathers gone?"

Causes of Father Absence

The physically and psychologically absent father of today is the product of sociological-cultural phenomena with the following roots: (1) The unity of the family is being continually sabotaged by external forces, some of which are controllable (ie, excessive television watching) and some far less controllable (ie, economic and career pressures requiring excessive commitments of the father's time). (2) Children must no longer depend on their fathers to learn certain technical or marketable skills. For that matter, there are so many "experts" that father's traditional educational responsibilities are often perceived as unneeded and frankly may be discouraged lest he teach the wrong tennis grip or some such other unpardonable error. In addition, many school-age children are kept so busy with extracurricular activities that the father often becomes reduced to a weekend administrator of his children's time and commitments. (3) Successful men in the sense of occupational achievement are home less often, and when they are home are frequently emotionally absent (fatigued, engaged in tension reducing hobbies, preparing business reports, etc). (4) As a consequence of the above, the father's visibility is less, his physical and emotional resources are drained, and, hence, his level of respect and authority have diminished. (5) Because of all these factors, the father's impact on the development of his children is less obvious, resulting in serious problems for many children.

Counseling the Father

This article will not concern itself with the arguments pro or con the father's investment in his job, career, or hobbies. Family counseling techniques suggest that if the father truly values these things, especially his career, the counselor should not initially encourage the father to diminish these activities in the interest of family growth and better child relationships. Too often the message to the father when this is done is that the counselor doesn't support what father considers important. In that case, the counselor (pediatrician) loses credibility. Nevertheless, there is very definitely a role for the pediatrician when fathering has been "dethroned" and is causing difficulties for the child and his family. To facilitate father involvement, the pediatrician might consider the following suggestions:

1. Be knowledgeable as to the

transformations of the American family and be realistic as to the tremendous external pressures that insidiously devitalize fatherhood. Advice that conceptualizes families as living in a vacuum is fundamentally ignorant and insulting. A valuable, up-to-date resource to help understand the complexities of the modern family is the recent publication by Kenneth Keniston and the Carnegie Council.[3]

2. Effective fatherhood begins in the prenatal period. The prospective father's degree of concern for the physical and emotional health of his pregnant wife as well as for his unborn child can be an effective barometer of postnatal parental involvement with his child. Paternal bonding has not been paid nearly the attention it deserves. Obstetricians and pediatricians should strongly encourage a prenatal pediatric visit, childbirth education classes, and, when they are offered, preparation for parenthood classes for both husband and wife. Pediatric house officers' participation in these activities should also be encouraged and would be of great educational value.

3. When a child has a complex biomedical, behavioral, or learning problem, the father should attend and participate in the initial diagnostic interview. It must be made clear to the father that whether the problem is cystic fibrosis, a sleep disorder, or a learning disability, he has an important role as a cotherapist with his wife in the management of his child's problems.

The father must learn from the therapist the ingredients of the therapeutic process. The pediatrician must not content himself with the fantasy that the father will learn the necessary treatment interventions from the mother. Husbands can't teach wives to drive; wives can't teach husbands to diaper. So, why should we assume that fathers can effectively learn from mothers the emotionally and physically demanding techniques that are used in behavioral therapy, such as time-out procedures, appropriate homework compliance for school learning disorders, and various mechanical interventions, eg, percussion and postural drainage for the child with a chronic pulmonary problem?

Much grief, confusion, and poor compliance could be avoided if pediatricians would insist on father's routine attendance at his office when these complex problems are discussed. A short evening clinic for families could facilitate the father's participation when his job makes daytime physician visits impossible.

4. Many fathers of children with chronic handicaps see only the aberrant behaviors that disorganize the home, fail to see strengths within the child, and fail to understand how the child feels about his particular disability. For example, children with learning disabilities are often anxious, depressed, and angry because of their frequent embarrassments in school and limited successes. Fathers may see only the outward behavioral manifestations of those feelings.

The counselor may help the father gain some insight into how his child feels by having the father identify an activity that he finds difficult and personally embarrassing—for example, singing in public—and then having the father visualize himself in situations where the activity is stressed constantly. This is analogous to the child with dyslexia who cannot read but is continually put in situations where reading is stressed and highly valued. Using imagery, the father might perhaps better understand how he would feel when put in situations where he cannot achieve, and might realize the resources he would need from within his family to give credibility to his strengths and other valuable aspects of his personality.

5. A successful counseling technique that often assists the father and child to learn to appreciate one another is orchestrating a way for the child to "tune in" to a craft, hobby, or activity that the father enjoys and values. It should be emphasized that the activity must be something that the father values. Asking a father to engage in activities with his children from which the father derives no pleasure, feels uncomfortable, or poorly competent, is fraught with difficulties. Begin with an activity that the father is good at, values, and is an arena of success for him. This gives credibility to the recommendation.

To initiate this process, it helps to tabulate a hobby or special interest inventory on the father. The skill of the pediatrician is then needed to help formulate a mechanism, with the father's help, as to what activities might be appropriate for the child, how the child might participate, and to what degree.

6. Since fathers often find value in their careers, it is helpful, as one of the initial steps in a troubled father-child relationship, to assist the child in understanding the father's job or career. Today, the father's job is much less visible and comprehensible to his children. What is amazing about so many of our present youngsters is how little they know about what their fathers do for a living. However, going to work with dad, if only to meet him for lunch, can be a revitalizing experience.

A colleague related these experiences of his own childhood:

> One of my fondest memories of childhood was occasionally accompanying my father to work on Saturday mornings. My father supervised a furniture factory, and as I would accompany him on his rounds, I could tell that he was totally and naturally immersed in his own element and enjoying every minute of it. The respect he received from his co-workers was obvious and some of this filtered down to me because I was his son. I grew to understand and value my father in new ways from these experiences.

COMMENT

Today's parents are unsure of themselves. Many of the old ways don't seem to work, and guidance often seems evasive or ambiguous. Parenting never was paradise, but parents are more frequently seeking advice from primary care physicians and pediatricians who often are inadequately prepared to offer effective, individualized parenting suggestions.

The role of the father in families is paid scant attention in pediatric education. Encouraging the father's optimal participation in family growth is both a legitimate and necessary role for pediatricians.

Conclusion

This article was written primarily as a commentary in hopes that it might serve as a catalyst for more interest and involvement within pediatric education as to the impact of fathers on their children and how the pediatrician relates to those experiences. Many issues have been left untouched: The father as primary caretaker, adoptive fatherhood, fathers who remarry, when the father dies, when a father divorces or deserts, and the mentally or physically disabled father. These are all common and troublesome problems. A suggested reading list to enhance interest and involvement of the pediatricians and pediatric educators appears below.

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The Impact of Ambulatory Pediatric Research on Changing Behavior

My father, as I am sure many of yours, has over the years been skeptical, if not outright critical, of some of the decisions I have made, and of some of the activities in which I have engaged. I have not always responded positively to his judgments or else I would never have left New York City to practice in the Finger Lakes region of upstate New York. However, I have always considered his viewpoint seriously because he has always approached things rationally and because he is a businessman, with a different perspective than mine. For example, he saw no logic in my leaving a well-established practice after 12 years to join the faculty at the University of Rochester. And after I had been there a year and had been awarded my first federally funded research grant, he had some rather insightful questions to ask about that activity. Those questions are ones we all need to consider seriously when we invest our time and efforts and other people's monies in seeking answers to the questions to which our research is directed.

He wanted to know what I was going to investigate, why I wanted to do that, and why the government wanted to invest in the project. He accepted my answers to those questions without comment.

Of course, he wanted to know how much money was involved—he was impressed. Then, how long the research would take. Three years seemed awfully long to him and the amount of money less impressive. He asked what would happen when the research was completed. *A report would be written.* And then? *Hopefully it would be published.* Where? *Probably a pediatric journal.* Circulation? *Twenty to 30 thousand.* How many of those who get the journal will read the report? *I don't know, maybe one, two thousand.* He wasn't finished. He saved the best question for last. What will they do after they read what you have written? I couldn't answer him. This, of course, is the $64,000, or, in this case, the $168,000, question—the question we do not often seriously consider: Will the results of our research change anybody's behavior?

Before we explore that last question further, I would like to look at the answers to some of those questions that led us up to it. These are important to our understanding of behavioral change resulting from new knowledge.

The motivation for research rests

with each individual. It ranges from the need to know answers to specific questions concerning health and illness and the health services system to responses to requests for research proposals, primarily because of the financial support they would provide the investigator. Then too, faculty may conduct research because of the creditability it provides within academia, or because of the intellectual kick it generates.

The specific area of research entered usually depends on one's interests, one's opportunities, and the relevance of the research question to those interests. An individual's interests, in turn, depend on the present and past influences of teachers, colleagues, readings, and patient care contacts.

We can determine the research interests of the members of the Ambulatory Pediatric Association who have a major commitment to research on ambulatory pediatric issues by reviewing the abstracts they have submitted for consideration of presentation over the years.

From 1935 through 1978, a total of 1,260 abstracts were submitted. Of these, 333 (26%) were selected for presentation at the annual meetings of the Ambulatory Pediatric Association (APA). The APA has had a formal scientific program since 1961, but no record of the number of papers submitted prior to 1965 is available.

The subjects of these 1,260 abstracts are too numerous to list even when placed into subcategories. However, if we use large "type of study" groupings, we can get some idea of the research interests of the APA membership. The Table provides us with a distribution of study types during the first and second halves of the past decade for papers presented. The distribution for all of the abstracts submitted is similar to that for those presented except that there were more descriptive analyses (59%) and less comparative analyses (6%) represented.

The "other" category shown in the Table, accounting for 5% of all abstracts submitted over the ten years, includes the development of research, educational, and screening instruments and methodologies; acquisition of educational and service program planning data; descriptions of specific diseases and their management; and attitudinal surveys.

It must be noted that the categorization of each study is based on its brief description in the submitted abstract. Experience in listening to individual presentations tells us that often such descriptions are not an accurate reflection of what was actually done.

It is obvious that most of the studies were descriptive and analytic, and few experimental or evaluative. One of the abstracts submitted by Pless and Roghmann[1] made this point about a sample of ambulatory pediatric research papers that had been published.

The specific subjects of the studies presented during the past decade covered the entire spectrum of ambulatory teaching, patient care, and research activities. Teaching programs were most frequently studied (19%), while innovative patient care programs (13%) and management of specific problems (9%) were next most frequently reported on. The frequency with which studies of allied health professionals were presented fell from 16% in the 1968 to 1972 period to 3% between 1973 and 1977, as did studies on comprehensive care programs (12% to 0%) and primary care practice (9% to 3%). On the other hand, presentations of studies on patient and parent characteristics rose from 3% to 19% between the same time frames

Of course, in order to allow for research to change behaviors, the publication of the results of one's work is necessary. There are very few data on what the likelihood is of research results being published.

In 1974, North[2] conducted his fourth survey of authors of abstracts submitted to the APA from 1965 through 1973 to determine the numbers that had been published. He found that of 609 abstracts submitted, 164 (27%) were presented and 154 (25%) were published. The 25% figure for published papers is on the low side as some of the 1972 and 1973 papers still had a reasonable chance at publication at the time the survey was made.

Although we cannot be sure, it seems that from 1965 through 1969 at least as many read-by-title papers were published as were presented papers. This may also be true for subsequent years, although North's data are not clear on this point.

Heagarty reported in her 1977 presidential address to the APA (unpublished data, April 1977) that, on the average, 94 papers were published annually over the past five years by APA members. It is obvious that all of their research efforts are not submitted for presentation at our annual meetings.

Research in ambulatory pediatrics is directed toward a specific end—improvement in patient care outcomes—just as is research in all biomedical fields. It is true that some basic biomedical research is unrelated to the solution of a clinical problem; however, there is an implied, if not stated, purpose of improving the well-being of mankind. For example, scientists whose main research goal is to learn how living organisms function without regard to the immediate relation to specific human diseases have contributed as much or more to our understanding and management of health and illness in humans as have those who have directed their research to the solution of specific clinical problems. Comroe and Dripps,[3] in a study of the research base of the ten most important clinical advances in cardiovascular and pulmonary diseases, found that 62% of the studies that contributed to these clinical advances were nonclinical.

It is unlikely that ambulatory pediatric research would ever become as serendipitous as this example. Our research is planned and controlled, with specific questions to be answered. Nevertheless, we need, as do all scientists, to move toward solutions to problems and to the acquisition and accumulation of knowledge that will assist us. These solutions ordinarily do not occur in one step or as the result of one research project. Thus, we must disseminate and store what Romano[4] terms our cumulative knowledge so that others working to the same end now and in the future can reach that goal most efficiently without retrac-

ing steps taken by others. This requires a system of adequate communication between them and those who are involved in patient care.

In this regard, we need to ask ourselves, "After publication, what then?" Is there any way we can answer my father's question, "Will the results of our research change anyone's behavior?" There are few or no data on this point. We can assume that change occurs from some research results without question. The work of Frankenburg and Dodds,[5] describing the Denver Developmental Screening Test, is a good example. We all can think of specific papers we have heard presented and of research results published in our favorite journal that have changed our own behavior In reviewing the abstracts submitted and presented to the APA, I made a conscious effort to answer the question, "Did the information presented in any way change my behavior?" The answer was positive in 3%. That, of course, is a subjective datum with no demonstrated validity and, in addition, I do not know whether I was influenced by the initial presentation, reading the abstract per se, reading the paper in published form, or because one or more of my colleagues influenced me directly or indirectly on the matter. Nor can I say how long it took me to act on the information once I had assimilated it. There are few data on this aspect of communication of innovations as well.

Roland and Kirkpatrick,[6] in studying the time lapse between hypothesis and publication in medical sciences, reported that the average time required from idea generation to publication was two years for case reports, three years for literature reviews, and four years for basic science and clinical research. Twenty-five percent of that time was required for journal handling.

We don't know how much time elapses between idea reception and change in behavior.

Rogers and Shoemaker[7] tell us that all explanations of behavioral change in humans have their basis in the means by which knowledge is acquired through communication. Mass media channels (not often open for the dissemination of new medical information) are often more important at creating awareness–knowledge of a new idea–whereas interpersonal channels are more important in changing attitudes (and behavior) toward adopting innovations. According to Becker,[8] "A professional's desire to maintain or increase prestige and professional status ... motivates him in his selection of information sources and adoption times." He recommends that if one is anxious to increase the adoption rate and decrease the adoption time, one should expose the opinion leaders in one's professional circles early on.

Types of Studies Selected for Presentation at the Ambulatory Pediatric Association's Annual Meetings, 1968 to 1977

Type of Study	% Distribution 1968-1972 (N = 139)	% Distribution 1973-1977 (N = 129)
Descriptive analyses	50	45
Intervention effectiveness	14	8
Comparative analyses	12	13
Epidemiologic surveys	6	5
Diagnostic methodology	6	7
Systems analyses	4	9
Predictive data analyses	4	8
Other	4	6

This is a difficult task, and we may wonder if it is the responsibility of the researcher to do this. We have the model of the "detail man" utilized by drug companies to disseminate information to practitioners. They are quick to quote prestigious medical persons in support of the use of a drug, perhaps with good reason.

In a study of implementation of new ideas generated by two investigations conducted in Rochester, NY, Dr Thomas McInerny and his colleagues (unpublished data) found that there was some evidence to indicate that a letter from the department chairman and a visit from a communications specialist–both designed to inform or reinforce clinical faculty awareness of the information in question–did result in behavioral change. This was, however, an expensive exercise not likely to be utilized in a nonexperimental situation.

Conceivably, one might obtain federal monies to implement such a communication process for significant research innovations. This, of course, would raise questions of what was significant, and the granting process, as we know, can be prolonged.

I do not want to suggest that because there are difficulties with the rapid dissemination of new ideas and with their adoption in practice that one should cease to be involved in conducting research. Worthwhile innovations in patient care will eventually be adopted–as will poor innovations. I mean only to examine the problems of communication of innovations and to suggest that we enter into the research arena with our eyes open and with some understanding of the answers to two questions, "Why am I doing this?" and "Will what I discover change anyone's behavior?" The answer to the first should be, "Because, in some way, the results of the study have the potential to improve the health of children." The answer to the second is always uncertain.

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Research Needs in Pediatric Nephrology and Urology

The defining characteristic of pediatric research is its concern with human development, the effect of changes that occur over time in the structure and function of biological and psychosocial processes. Thus, research in pediatric nephrology and urology includes developmental studies, and it focuses on diseases that have altered manifestations or therapeutic requirements in the pediatric age group. The diseases and conditions reviewed here are limited to those that fit within these definitions.

DEVELOPMENTAL ABNORMALITIES

Developmental abnormalities are responsible for some of the major clinical problems in pediatric nephrology and urology. Until recently, the general perception of developmental abnormalities was restricted to obvious physical anomalies. This limitation resulted in a severe underestimation of the magnitude and scope of the clinical problems due to aberrant development. It is now recognized that developmental abnormalities at the enzymatic and molecular levels are responsible for many biochemical and physiological disturbances, some of which produce serious clinical problems.

Morphogenesis and Malformation

An understanding of maldevelopment requires knowledge of normal development. The elaboration of urine probably commences with vascularization of the earliest glomeruli, and a flow of fluid is probably necessary to normal anatomic modeling of the kidney. Renal tubules in both human and animal fetuses undergo rapid ultrastructural differentiation, even though enzymic and functional studies have shown "immaturity." Studies of substrate and hormonal stimulation of function strongly emphasize the role of extrarenal and environmental factors.

Among the most common and best known types of renal maldevelopment are renal dysplasia and bilateral cystic disease. The kidney in renal dysplasia is abnormal both in structural organization and in cellular differentiation. Renal dysplasia is a relatively common abnormality that is encountered in approximately 1.5% of pediatric autopsies; it accounts for 20% of all urinary tract malformations. Renal dysplasia commonly complicates congenital lower urinary tract obstruction, and its patterns correlate with different types of obstruction in a manner suggesting causal relationships. Nonobstructive dysplasia occurs in many syndromes of multiple malformation, presumably as the result of interference with normal renal development by heritable factors. Dysplasia kidneys, which are also frequently cystic, constitute the most frequent form of bilateral cystic disease in newborn infants. Polycystic disease, on the other hand, appears to be an abnormality that can arise both during nephronic development or after tubules have formed completely. Experimental studies clearly demonstrate that diffuse cystic disease is not necessarily due to embryonal maldevelopment and that the abnormality may be produced postnatally in previously normally developed kidneys.

A common trend, therefore, can be found in renal dysplasia and renal polycystic disease. In each of these conditions, there may be a basic element of ductal and nephronic injury with cyst formation. The cause of injury may be urinary obstruction, genetically altered metabolic pathways, or other undefined factors, but the renal injury itself appears most often to be secondary rather than primary and intrinsic.

A suitable experimental model for the study of renal dysplasia and the evaluation of contributing factors, such as urinary tract obstruction and

metabolic injury, needs to be developed. The agents responsible for polycystic disease need to be identified to develop appropriate and pertinent laboratory models that can be used for studies of renal function, pathogenesis, and thereapeutic intervention. Studies of embryonic induction and morphogenesis should be continued to define the nature of induction, the processes of development and maturation, and the responses of the kidney to workload and to substrate-specific and hormonal stimulation.

Glomerular and Tubular Basement Membranes

Several renal diseases, some acquired and some heritable, are associated with alterations in the chemical composition and molecular arrangement of the glomerular basement membrane (GBM). In some heritable disorders, eg, diabetes mellitus, the chemical alterations in the GBM are probably secondary. In others, the defects may be related to primary abnormalities in the molecular biology of basement membranes. Ultrastructural studies suggest a structural abnormality of the GBM in Alport's syndrome, in the nail-patella syndrome, and in diabetic nephropathy. The GBM may also be abnormal in "minimal change" nephrotic syndrome despite lack of evidence from ultrastructural studies. The abnormalities in GBM that result in proteinuria, hematuria, and often lead to renal failure may be due to alterations in either the synthesis or catabolism of basement membrane glycoproteins. The role of tubular basement membranes in susceptibility to injury, especially from infection and reflux in childhood, is unknown.

Although investigations into membrane chemistry suggest that alterations in biosynthesis may play a significant role in renal disease, developmental aspects of these processes have been neglected. The roles of nutritional and environmental factors, drugs, chemicals, infection, and metabolic factors at different stages of malnutrition, and the response of glomerular and tubular membranes to hypoxia, drugs, chemicals, and other environmental hazards at different stages of maturation should be studied.

Renal Tubular Abnormalities

Abnormalities of renal tubular function are among the most frequently occurring genetic disorders in childhood. The abnormalities include derangements of amino acid, sugar, phosphate, and hydrogen ion transport. Recent programs for testing urine of newborns for hypersecretion of amino acids indicate that cystinuria, Hartnup disease, and iminoglycinuria may be detected in 1 in 7,000, 1 in 12,000, and 1 in 14,000 live births, respectively. When renal glycosuria, Fanconi's syndrome associated with cystine storage, galactosemia, fructose intolerance, hypophosphatemic rickets, and renal tubular acidosis are included in the list, the incidence of these inherited tubule disorders is of the order of 1 in 1,000 births.

These entities are functional disorders of the renal tubular membrane and, as such, constitute important newly defined forms of renal disease. Their understanding must be based on an intimate knowledge of the structure and function of normal renal tubular membranes. Current concepts hold that genetically determined protein molecules within the membrane exist for facilitating movement of solutes across the membrane, as in the processes of reabsorption of electrolytes, amino acids, sugars, and phosphates from the glomerular filtrate. The isolation and characterization, the synthesis, and the placement in the lipid membrane of these transport carriers need to be studied; the coupling of the transport processes by ions and hormones are important aspects for future research. The investigation of tubular membranes requires animal models with defects comparable to those in man.

Urological Anomalies

Developmental anomalies give rise to a variety of urologic diseases. Hypospadias is an arrest in the normal development of the phallus and urethra, probably caused by inadequate secretion of testosterone or a testosterone-like substance by the fetal testis; cryptorchidism is sometimes caused by inadequate hormonal secretion. Other causes of incomplete descent (ectopia) include impaired testicular responsiveness to gonadotrophin, and anatomic obstruction.

Developmental abnormalities of the cloaca give rise to exstrophy of the bladder and to epispadias. Hydrometrocolpos is commonly associated with ureteral obstruction, because the ureteral bud arises in an abnormal location instead of from the normal position that corresponds to the later site of the ureteral orifice in the bladder. Anomalies of the ureteral bud also give rise to ureteral obstruction when the ureter opens into the seminal vesicle or the posterior urethra, or when it is associated with a ureterocele. In such instances, the faulty ureteral bud often induces a hypoplastic or dysplastic kidney.

An understanding of the effects of vesicoureteral reflux on renal development in the fetus and on renal growth in childhood is important to the understanding of the morbidity of urinary tract infection. Reflux nephropathy may be responsible for both hypertension and renal failure in children.

Studies are needed on the transmission and pathogenesis of these disorders to screen patients selectively for those at risk, on methods to identify urinary tract obstruction early to allow for reconstructive surgery in preventing progressive renal damage, and on the causes and treatment of urinary incontinence, which is a socially debilitating disease, particularly in the growing child, who quickly becomes a pariah. Mechanical sphincters that can be easily adjusted to accommodate to changes in the size of the growing child could be implanted earlier, with beneficial effects on the social development of the incontinent child.

ASPECTS OF RENAL AND UROLOGIC DISEASES PECULIAR TO CHILDREN

Neonatal Renal Diseases

It is known that major changes in renal blood flow and its intrarenal distribution take place during the first months of life, and it is suspected that these changes in turn control the rapid changes in renal function that

take place after birth. Functional renal impairment in the neonate presumably relates to disturbances in renal circulation in the respiratory distress syndrome, in erythroblastosis, in infants undergoing major cardiac surgery, and in infants of diabetic mothers. The relationship of specific antecedents, such as hypoxia and hypotension, to renal cortical and medullary necrosis is poorly defined, but diminished renal cortical perfusion may be a common event. The relationship of renal injury in the neonatal period to disease manifesting later in life is unknown.

Investigation is needed of factors that control renal blood flow in the fetus and the factors responsible for changing patterns of blood flow postnatally.

Hereditary Nephritis

Many forms of hereditary and familial nephritis are now recognized, although the basic defect in none of these has been identified. Recent electron microscopic observations in Alport's syndrome and in the nail-patella syndrome suggest primary abnormalities in the synthesis or arrangement of basement membrane collagens. Hereditary renal disease is heterogeneous, possibly representing structural defects, metabolic disorders, abnormalities in membrane composition, and immune disturbances. Some of these disorders are manifest in infancy, others not until later in childhood or adolescence. Although they commonly progress to end-stage renal failure, methods of treatment are unknown.

Future research should center on identifying nephrotoxic metabolic disorders that may be responsible for the renal lesions in hereditary nephropathies, including medullary cystic disease, familial juvenile nephronophthisis, hereditary progressive nephritis, and congenital nephrotic syndrome.

Congenital Nephritis and Nephrotic Syndrome

The congenital nephrotic syndrome occurs with increased frequency in certain ethnic groups, but its etiology and pathogenesis remain unknown. We do know that there are several histologic types of glomerular abnormality in the congenital nephrotic syndrome and that they appear to have differing genetic and prognostic implications. Treatable glomerulonephritis (eg, congenital syphilis and congenital toxoplasmosis) appears to have no effect on subsequent development of the kidney, but a nagging concern remains. Similarly, the basis for the consequences of early infantile, bacterial pyelonephritis, which is predominantly a disease of males, remains to be clarified.

Identification is required of the mechanisms by which hereditary abnormalities, perhaps with activation of immune mechanisms, injure the kidney secondarily to result in congenital nephritis and nephrotic syndrome.

Responses of Children and Their Families to Pediatric Renal and Urologic Diseases

Children with renal and urologic disease present two problems relating to growth and development. One is that chronic disease or severe acute disease may alter developmental processes and lead to growth or developmental retardation. The second is that disease manifestations or therapeutic responses well described in adults often are different in children.

Retarded statural growth is a matter of great clinical importance to a child. Sexual maturation is a major milestone in development; if delayed or significantly modified, the consequences may be devastating. Both growth and sexual retardation affect social maturation, which refers to the capacity of the child to mature and to assume an independent self-sustaining state as an adult. Other factors of importance include ways in which the disease affects learning, lack of socialization among peers, and the manner in which those on whom the child is dependent adapt to the child's disability.

The nutritional and metabolic factors that are associated with poor growth in children with renal disease need to be studied, including factors that may underlie energy or protein metabolism and their relation to nutrition, and micronutrients, of which zinc may be particularly important. *Safe* and *effective* techniques for nutritional therapy are needed.

The control of skeletal and muscular growth in children with renal disease, including muscle wasting, and osteodystrophy, and acidosis as causes of growth failure, need to be investigated. The roles of potential catabolic hormones, cortisol, and catecholamines need to be identified and a possible link between growth failure, physical conditioning (muscular activity), and emotional stability should be studied.

The impact of chronic disease on the psychosocial maturation of children needs investigation to assess how attitudes of the family and others or societal values enhance or limit a handicapped child's drive for independence; to develop techniques that are useful in the child's developing skills for living; and to determine how a child can willingly cooperate with a complex chronic treatment program and develop independence. Studies are needed also to learn how chronic renal disease affects siblings, parents, and medical staffs; anecdotal evidence strongly suggests that families are severely affected by chronic illness in a child and need extensive care far beyond treatment of the specific disease.

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These comments summarize one part of a series of reports that constituted an Evaluation of Research Needs in Nephrology and Urology by the Specialty Committee on Pediatric Nephrology and Urology. Committee members are as follows: Henry L. Barnett, MD (*chairman*), New York; Jay Bernstein, MD, Royal Oak, Mich; Chester M. Edelmann, Jr, MD, New York; Malcolm Holliday, MD; San Francisco; Lowell King, MD, Chicago; Bernard Lytton, MD, New Haven, Conn; Rawle McIntosh, MD, Denver; Stanton Segal, MD, Philadelphia. Copies of the complete report are available from the National Institute of Arthritis, Metabolism, and Digestive Diseases, Bethesda, Md.

Articles

Trimethoprim-Sulfamethoxazole vs Sulfamethoxazole for Acute Urinary Tract Infections in Children

Jorge B. Howard, MD, Jorge E. Howard, Sr, MD

• A total of 118 children between 6 months and 10 years of age with acute urinary tract infection were treated in a random; double-blind manner with 12 mg/kg/day of trimethoprim-sulfamethoxazole (61 patients) or 50 mg/kg/day of sulfamethoxazole (57 patients) for ten days. Mean trimethoprim and sulfamethoxazole susceptibilities of *Escherichia coli* isolated from these patients were 1.2 and 0.6 μg/ml, respectively. Mean serum concentrations of trimethoprim and sulfamethoxazole were 1.8 and 62 μg/ml, respectively, one hour after the dose. Of the children who completed the ten days of prescribed medication, clinical and bacteriological cure was confirmed immediately after treatment for all but one patient in each group. Most patients in each treatment group with recurrent infections had underlying urological abnormalities. Severe hematological, renal, or hepatic toxicity requiring interruption of treatment was not encountered. No advantage of trimethoprim-sulfamethoxazole over sulfamethoxazole alone for acute urinary tract infection was demonstrated.

(*Am J Dis Child* 132:1085-1087, 1978)

Sulfonamides are the most frequently recommended drugs for treatment of acute urinary tract infections in infants and children. *Escherichia coli* and other coliform bacilli causing these infections are usually susceptible to sulfonamides. The combinations of trimethoprim, an inhibitor of dehydrofolate reductase, with sulfamethoxazole has been claimed to produce better therapeutic results in adults, especially in those situations in which there is a substantial incidence of sulfonamide-resistant strains of *E coli*.[1,2] To assess the possible superiority of the combination of trimethoprim-sulfamethoxazole over sulfamethoxazole alone in the treatment of acute urinary tract infections in children, the following study was undertaken in the outpatient clinic of Children's Medical Center, Dallas.

PATIENTS AND METHODS

Infants and children of either sex and of any ethnic background with acute urinary tract infection who could be kept under medical observation for 42 days were enrolled in the study. Patients were between 6 months and 10 years of age. They had developed symptoms and signs of acute urinary tract infection within 72 hours and had not taken any antibacterial medication within the previous week. Children with chronic or recurrent urinary tract infections were excluded.

At the initial visit, a history and physical examination, determination of complete blood cell count, SGOT level, and serum creatinine level, routine urinalysis, and urine culture were done. In infants under 2 years of age, urine for culture was obtained by suprapubic bladder aspiration. In the older children, a clean-catch, midstream urine specimen was used for culture.

Patients were assigned to drug therapy according to a randomization table, and medication sufficient for three days was given. Children weighing less than 30 kg were given pediatric suspension and those over 30 kg were given tablets. Both study drugs were given in a random, double-blind manner at a daily dosage of 10 to 12 mg/kg of trimethoprim and 50 to 60 mg/kg of sulfamethoxazole in three equally divided doses for those treated with the combination drug and 50 to 65 mg/kg/day in three equally divided doses for those treated with sulfamethoxazole alone.

Urine for culture was inoculated onto 5% sheep's blood agar and eosinmethylene blue agar media and incubated overnight at 36 °C. The diagnosis of urinary tract infection was established when the quantitative culture of clean-catch midstream urine was at least 10^5 colony-forming units per milliliter.

Disk susceptibility antimicrobial testing was performed by the disk method of Bushbey[3] in which minimal inhibitory concentrations are extrapolated from zone diameters.

Of the 229 subjects enrolled, 118 were retained in the study after the third day. The others failed to return (44 patients), the initial urine culture was negative (52 patients), or they had not taken their medication (15 patients). Those retained in the study were given medication for an additional seven days.

Seven, 14, and 42 days after onset of therapy, the patients were reexamined, and urinalysis, urine cultures, complete blood cell counts, and platelet counts were done. Treatment was considered a failure if cultures on days 7 or 14 had bacterial

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Reprints not available.

growth of the same genus and antimicrobial susceptibility as the initial culture.

Clinical and bacteriological cure was defined as absence of signs and symptoms of urinary infection and a sterile urine culture at the 14-day follow-up. Recurrence was defined as a urine culture with the same bacterial genus with the same susceptibilities as initially present at any time between days 15 and 42 after onset of treatment. If the bacterial genus or susceptibilities were different, it was called reinfection.

Intravenous pyelography (IVP) and cystourethrogram radiologic studies were done if urine cultures were positive at any of the follow-up examinations. The SGOT and serum creatinine determinations were repeated on day 14.

On the third day, serum specimens were collected from 14 patients one hour after receiving trimethoprim-sulfamethoxazole on the seventh day, serum was obtained from four patients three to five hours after a dose. The serum was kept at −20 °C. On day 7, a 10-ml aliquot of urine was obtained from 59 patients and frozen at −20 °C. Serum and urine specimens were shipped in dry ice to a laboratory, where concentrations of the drug in serum and urine were assayed using the Bushbey and Hitchings[4] microbiologic method for trimethoprim and Rieder's[5] method for sulfamethoxazole.

RESULTS

Sixty-one patients were treated with trimethoprim-sulfamethoxazole and 57 with sulfamethoxazole alone. The groups were comparable regarding age, sex, and symptoms (Table 1) except that a greater number in the combination drug group had fever (χ^2, 4.98; $P < .05$) and dysuria (χ^2, 7.63; $P < .01$).

Escherichia coli was the commonest etiologic agent (Table 1). The mean minimum inhibitory concentration (MIC) determined for 84 strains of *E coli* was 0.06 μg/ml of trimethoprim. The mean MIC for sulfamethoxazole was 1.2 μg/ml, with values between 0.29 and 2.85 μg/ml for all except two cases (7.35 and 9.50 μg/ml). Of the two *Streptococcus faecalis* strains, one was resistant and one was susceptible in vitro, yet both patients responded to treatment and did not have recurrence of infection.

The mean serum concentrations of trimethoprim and sulfamethoxazole in 14 patients one hour after receiving their medication on the third day of treatment were 1.84 and 62 μg/ml, respectively (Table 2). The concentrations of trimethoprim and sulfamethoxazole in randomly collected urine specimens were determined on the seventh day in 21 children receiving the combination drug and in 28 treated with sulfamethoxazole alone (Table 2). The mean urine concentrations of trimethoprim were more than 50-fold greater than the mean MIC for *E coli*, and those of sulfamethoxazole were twofold to threefold greater.

Seven of the 61 patients in the combination drug group did not keep their return appointments, and one was removed from evaluation because of lack of compliance. Nine of 57 patients in the sulfamethoxazole group did not return for follow-up. Two patients could not be evaluated, one because of vomiting and the other because of failure to take the prescribed amounts of medication. Thus, 53 patients treated with trimethoprim-sulfamethoxazole and 46 treated with sulfamethoxazole alone were evaluated.

Seven patients in the combination drug group had positive urine cultures on or after day 7 (Table 3). Of these, one was a patient with persistence of symptoms and positive urine culture on day 7 in whom no radiological study was done. Four children had recurrence of bacteriuria. The *E coli* strains were not serotyped so we could not

Table 1.—Clinical Characteristics of Treatment Groups

	No. (%) of Patients	
	Trimethoprim-Sulfamethoxazole (N = 61)	Sulfamethoxazole Alone (N = 57)
Age		
6-23 mo	12 (20)	13 (23)
2-5 yr	42 (69)	32 (56)
6-10 yr	7 (11)	12 (21)
Symptoms		
Increased frequency of urination	45 (74)	43 (75)
Fever	35 (57)	21 (37)
Dysuria	38 (62)	21 (37)
Malaise	38 (62)	40 (70)
Flank pain	26 (43)	33 (58)
Bacterial etiology		
Escherichia coli	54 (89)	53 (93)
Klebsiella pneumoniae	3 (5)	1 (2)
Enterobacter sp	2 (3)	1 (2)
Proteus sp	1 (2)	1 (2)
Streptococcus faecalis	1 (2)	1 (2)

Table 2.—Antimicrobial Assays of Serum and Urine

	Trimethoprim, μg/ml	Sulfamethoxazole, μg/ml
Serum		
1 hr after dose on day 3 (14 patients)		
Mean	1.8	62
Range	0.8-3.8	35-85
3-5 hr after dose on day 7 (4 patients)		
Mean	0.8	41
Range	0.4-1.3	28-81
Urine		
Day 7, 21 patients receiving trimethoprim-sulfamethoxazole		
Mean	115	139
Range	20-268	34-201
Day 7, 28 patients receiving sulfamethoxazole alone		
Mean	...	173
Range	...	32-405

Table 3.—Responses to Therapy

	No. (%) of Patients	
	Trimethoprim-Sulfamethoxazole (N = 53)	Sulfamethoxazole Alone (N = 46)
Urine cultures		
All follow-up cultures sterile	46 (87)	40 (87)
Positive during therapy	1 (2)	2 (4)
Recurrence of *Escherichia coli* infection	4 (8)	3 (7)
Reinfection	2 (4)	1 (2)
Adverse reactions to drugs		
Rash	1 (2)	0 (0)
Platelets <150,000/cu mm (day 7)	1 (2)	1 (2)
Platelets <150,000/cu mm (day 14)	3 (6)	4 (9)
SGOT > 50 units (day 14)	12 (23)	9 (20)
Hemoglobin decrease of > 2 g/dl	1 (2)	1 (2)

establish whether recurrence of *E coli* represented relapse or new infection. Three of these had abnormal IVP and/or abnormal cystourethrograms made while voiding, with massive ureteral reflux in one and uretropyelojunction distortion in two. One had a normal radiological study. Two patients with recurrent bacteriuria had a different bacterial genus cultured from that found originally and therefore represented new infections. In both patients, IVP and cystourethrograms were normal.

In the sulfamethoxazole group, six children had positive cultures on or after day 7. One was a patient with persistence of symptoms and positive culture on day 7 in whom the radiological study demonstrated massive bilateral ureteral reflux. One other patient was asymptomatic but had a positive urine culture on day 7 and was shown to have a bladder neck obstruction. Three patients had recurrence of *E coli* bacteriuria. One had a normal IVP and a normal cystourethrogram made while voiding, another had a bladder diverticulum, and the third had considerable bilateral ureteral reflux. One patient had a new infection on day 42, with a different organism in the urinary tract; the IVP and cystourethrogram were normal.

On the ninth day of treatment, one child taking the combination drug developed a morbilliform rash that lasted three days (Table 3). On day 14, three children in the trimethoprim-sulfamethoxazole group and four in the sulfamethoxazole group had fewer than 150,000 platelets per cubic millimeter. Depressed platelet counts ranged from 52,000 to 139,000/cu mm. The hemoglobin level was 2 g/dl lower than on day 0 in one child in each group. The SGOT level rose to greater than 50 IU in 12 children treated with the combination drug and in nine who received sulfamethoxazole alone. The abnormal results returned to normal on determinations made on the 42nd day.

COMMENT

As in all studies of acute urinary tract infections in the pediatric age group, ours found *E coli* to be the preponderant etiologic agent and also showed the clinical efficacy of sulfonamide therapy in a large proportion of cases. The bacterial isolates were susceptible to concentrations of sulfamethoxazole obtainable in serum and in urine.

Clinically and bacteriologically, the addition of trimethoprim to sulfamethoxazole did not prove superior to sulfamethoxazole alone. This was also noted by Feldman et al,[6] who treated 13 children for urinary tract infection with sulfamethoxazole alone and 13 with trimethoprim-sulfamethoxazole for a four-week period. In a 12-month follow-up period, the difference in the recurrence rates between their groups was not significant.

In most patients considered failures or relapses, the IVP and cystourethogram, done two to three weeks after the urine cultures became negative, showed anatomical or functional abnormalities.

We did not encounter any serious toxic effect with the trimethoprim-sulfamethoxazole combination. One child had a rash possibly due to the drug. Depression of platelets occurred equally often with sulfamethoxazole as with the combination drug. No clinical bleeding problems were observed and platelet counts returned to normal after cessation of therapy. Böse et al[7] similarly found that platelet counts fell below 150,000/cu mm in ten of 55 children.

This study demonstrated no advantage to the use of trimethoprim-sulfamethoxazole over sulfamethoxazole alone for treatment of acute urinary tract infection. In the population studied, there was a high frequency of sulfamethoxazole-susceptible organisms. In situations in which sulfonamide-resistant bacteria are common, the combination of trimethoprim and sulfomethoxazole could be used advantageously as an alternative treatment to sulfanamide drugs.

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Judy Hamilton, RN, and Susan Kubelka, RN, assisted with this study.

Nonproprietary Name and Trademarks of Drug

Sulfamethoxazole—*Gantanol*, *Gantanol DS*.

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Respiratory Syncytial Virus Infection

Rapid Diagnosis in Children by Use of Indirect Immunofluorescence

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• Specimens of 387 nasopharyngeal suction smears obtained from 354 children hospitalized with acute respiratory infections during an eight-month period were examined for the presence of respiratory syncytial (RS) virus by the indirect immunofluorescence antibody technique (IFAT) and by conventional tissue culture infectivity techniques. Respiratory syncytial virus was identified in nasopharyngeal suction smear specimens from 123 of these specimens (32%) with the use of both techniques. Of the specimens positive on tissue culture, 92% were also positive for RS virus by IFAT. However, eight specimens positive for RS virus by tissue culture were negative by IFAT, although three of the specimens were technically unsuitable. Six percent of the specimens negative for RS virus by tissue culture were positive for RS virus antigen when tested by IFAT. Using IFAT, identification of RS virus could be accomplished within four to six hours, whereas isolation by tissue culture took an average period of ten days. These data suggest that IFAT is a reliable means for the rapid diagnosis of RS virus infection in infants and children.

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Respiratory syncytial (RS) virus is the major cause of lower respiratory tract infections in infants and young children and as such accounts for a large number of admissions to pediatric wards.[1-8] Tissue culture techniques and serology comprise the standard diagnostic tools for diagnosis of RS virus infection in the virology laboratory. However, these techniques are hampered by delays of one to two weeks before an identification of the infectious agent can be made with certainty. Therefore, a definite need exists for the rapid diagnosis of RS virus and other respiratory viral infections in childhood.

Gardner and associates[9-11] described an indirect immunofluorescence antibody technique (IFAT) for the rapid diagnosis of RS virus in clinical specimens and have used it successfully in England since 1968. Nagahama et al[12] evaluated a direct immunofluorescence method in 1970 and found it to be an effective tool in the rapid diagnosis of RS virus. In addition, Fulton and Middleton,[13] reported a good correlation between IFAT and tissue cultures for detecting the presence of RS virus.

The present investigation was undertaken to evaluate the IFAT for the rapid diagnosis of RS virus in exfoliated cells in nasopharyngeal secretions.

MATERIALS AND METHODS

Patient Population

The study population consisted of 354 children who were hospitalized at the Children's Hospital of Buffalo during an eight-month period from November 1976 to June 1977. A total of 387 nasopharyngeal suction smears (NPS) were collected and multiple specimens were obtained from 30 patients. The subjects ranged from younger than 1 month to 18 years of age. The subjects were hospitalized with clinical diagnoses of bronchiolitis, pneumonia, acute asthmatic episodes, croup, or diffuse upper respiratory tract illness.

Specimen Collection and Processing

The NPS specimens were collected on the morning of admission using disposable plastic mucous traps. The NPS specimens were sucked into the mucous trap and the suction catheter was flushed with 5 ml of a transport medium (Hank's balanced salt solution with 0.2% of bovine serum albumin and antibiotics). The specimen was centrifuged at 1,000 rpm for ten minutes; the supernatant was removed and used for inoculation of tissue cultures for virus isolation. The cellular pellet was washed with phosphate-buffered saline and resuspended in a small volume of phosphate-buffered saline, and smears were made onto microscope slides. The NPS smears were air dried and fixed in acetone for ten minutes and stored frozen at −70 °C.

IFAT

The slides of NPS were incubated in a moist chamber with a 1:5 dilution of bovine anti-RS virus serum for 30 minutes at 37 °C.[14] The NPS smears were then incubated with a 1:10 dilution of fluorescein isothiocyanate (FITC) conjugated antibovine immunoglobulin in 0.005% of Evans blue counterstain for 30 minutes at 37 °C. Extensive washing procedures in PBS were used after each incubation. A final wash in distilled water was used before the slides were air dried and examined. A

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negative control using normal bovine serum in place of the bovine anti-RS virus serum was included with every specimen. A positive control using RS virus-infected Hep 2 cells was used with each experiment. The stained slides were examined using an epi-illumination system. Photographs were made using ASA 200, 35-mm slide film with exposures that varied from two to three minutes.

Before the test system could be used in a clinical setting, several control experiments were done to assess the sensitivity and the specificity of the technique. The bovine anti-RS virus serum and antibovine FITC conjugate were titrated using IFAT to determine the optimal dilution of both reagents that gave maximum specific fluorescence for RS virus-infected HEp 2 cells and minimum nonspecific fluorescence with uninfected HEp 2 cells. At the optimal dilution of the antisera, at least 50% of the RS virus-infected HEp 2 cells showed a positive fluorescence of 3+ to 4+ intensity. Each new batch of reagents required such calibration before use. HEp 2, rhesus monkey kidney, and WI-38 cells infected with a wide range of viruses, including parainfluenza 1, 2, and 3, adenovirus, influenza, and RS virus, were tested in the RS virus-IFAT system to ensure the absence of cross-reactivity of these reagents with the other viral agents. Positive fluorescence was seen only with the RS virus-infected cells. The staining of RS virus could be effectively blocked by treating the NPS smears with human antibody to RS virus before staining the slides with FITC-labeled antisera to bovine immunoglobulin. As additional controls, antisera to adenovirus and parainfluenza 1, 2, and 3 gave no staining reactions with RS virus-positive smears. No staining reactions were seen in uninfected tissue cultures used as negative controls.

Tissue Culture Infectivity (TCI)

HEp 2, primary rhesus monkey kidney, and WI-38 cell cultures were used for routine virus isolation.[15] Neutralization with type-specific antisera was used for confirmation of the adenoviruses and enteroviruses while rhinoviruses were identified by the acid stability test. Hemadsorption of the cell cultures was performed to detect influenza and parainfluenza viruses.[15]

RESULTS

Characteristics of IFAT Staining

The immunofluorescence seen was entirely intracytoplasmic in the form of particulate material that varied in size from fine particles to large, inclusion-like bodies. The nucleus was unstained. The presence of as few as two to three cells with such characteristic fluorescence on one smear was sufficient for diagnosis. However, most positive specimens contained at least one infected cell per microscopic field. An experienced observer could screen one specimen in ten to 15 minutes. The entire procedure of staining and examining the smear could be easily completed within four to five hours.

Comparative Evaluation of IFAT and TCI

Using both IFAT and TCI, RS virus was detected in 123 NPS specimens. The RS virus was isolated by TCI in 106 (27%) NPS specimens. The remaining 281 (73%) NPS specimens failed to yield RS virus by TCI (Table). Of the 106 NPS specimens positive for RS virus by TCI, 98 (92%) were also found to be positive by IFAT. However, eight TCI-positive specimens were negative for RS virus by IFAT. It should be pointed out that three of the IFAT-negative NPS smears were found to have an insufficient number (less than 2/high-power field) of exfoliated cells. Only five (4.7%) of the NPS specimens that were positive on TCI and contained adequate cells were negative for RS virus by IFAT (Table). Of the 387 specimens available for IFAT, only ten (2.5%) were considered to have an inadequate number of cells.

Ninety-four percent of the NPS specimens negative for RS virus by TCI were also negative by IFAT. However, it is of interest to note that 17 (6%) of the specimens negative by tissue culture were positive for RS virus antigen when tested by IFAT (Table). All such specimens were obtained on follow-up testing from subjects whose initial specimens were RS virus positive by both TCI and IFAT.

The cytopathogenic effect of RS virus in TCI was manifested as early as six days and as late as three weeks after inoculation. The average duration of time required for detection of RS virus by TCI was about ten days.

Comparative Evaluation of the Identification of Respiratory Syncytial (RS) Virus in Nasopharyngeal Suction Smears (NPS)

Tissue Culture Infectivity of NPS Specimens		Indirect Immunofluorescence of NPS Specimens: Positive for RS Virus No.	Positive for RS Virus %	Negative for RS Virus No.	Negative for RS Virus %
Total no. tested	387	115	29	272	70
No. positive for RS virus	106	98	92	5*	4.7
No. negative for RS virus	281	17	6	264	94.0

*Three other specimens were considered unsuitable for IFAT because of insufficient number of exfoliated cells.

COMMENT

Immunofluorescence has been used to confirm the presence of RS virus antigen in tissue cultures after the appearance of the characteristic cytopathic effect and has replaced the tedious neutralization test in several laboratories.[9-11] However, up to two weeks might elapse for sufficient growth in tissue culture before this technique can be used.

Gardner and associates[9-11] used IFAT to detect RS virus in exfoliated nasopharyngeal cells from children with acute respiratory infections and found it to be rapid and sensitive. In North America, the direct immunofluorescence technique worked well for Nagahama et al,[12] and Fulton and Middleton[13] reported similar results. Despite the availability of this laboratory tool since 1968, it has not been regularly used by diagnostic laboratories in North America.

In the present study, IFAT was selected because of the fourfold to 12-fold increased sensitivity of this technique over the direct fluorescence.[16,17] In addition, one fluorescein-conjugated antiserum could be adapted for use in the rapid IFAT diagnosis of a variety of viral agents causing

respiratory infections, such as parainfluenza 1, 2, and 3, influenza A and B, adenovirus herpes simplex virus, etc.[14]

Sturdy et al[18] found NPS specimens superior to nasal swabs or cough specimens when used for detecting RS virus by IFAT because the latter contained fewer infected cells but many more squamous cells or polymorphonuclear leukocytes that produced nonspecific fluorescence. Hence, the NPS specimens were used exclusively in our investigation.

There were 17 specimens that showed positive fluorescence for RS virus but failed to yield the virus on tissue culture. Similar observations have been made by other workers[11,14] who inferred that such discrepancies may be due to the increased sensitivity of IFAT over the tissue culture system, particularly if the specimens have been obtained later than five to seven days after the onset of symptoms when the development of specific neutralizing antibody and decreasing virus excretion in the nasopharynx may reduce the TCI of the virus. The finding of eight specimens positive by tissue culture but negative by IFAT was not of major concern because three of the specimens were unsuitable for IFAT due to insufficient numbers of exfoliated cells. In our investigations, we encountered only ten specimens (2.5%) that had insufficient cells for immunofluorescence compared with 32% of such specimens seen by Fulton and Middleton.[13]

We found the IFAT to be a sensitive and specific test when applied in a clinical setting, with a 92% agreement with TCI procedures for positive specimens and 94% for the negative ones. For the past 18 months, we have been routinely using this approach for the rapid diagnosis of RS virus infection in our hospital. As a result, an increased awareness of the impact of RS virus in childhood respiratory infections has been established among physicians and nursing staff. Preliminary data suggest that the rapid diagnosis of virus infection in children with respiratory diseases has modestly reduced the indiscriminate use of antibiotics, particularly in cases of acute respiratory infection. An attempt has also been made to reduce the incidence of nosocomial infections by rapidly identifying and separating the patients with RS virus-associated respiratory diseases.

The efficacy of this test system depends on several factors. Adequate samples containing several exfoliated cells must be collected and promptly transported to the laboratory where they should be processed immediately. Careful attention must also be paid to the control of specificity of the reagents used in the IFAT.

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Pneumococcal Pneumonia With Pneumatocele Formation

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• **Two infants had pneumococcal pneumonia and bacteremia, complicated by pneumatocele formation. The pneumatoceles appeared during the recovery phase and were indistinguishable from those associated with staphylococcal pneumonia. Complete resolution occurred in both patients. Pneumatoceles occur in pneumonias caused by varied agents; therefore, determination of the cause is imperative for appropriate therapy.**

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Pulmonary pneumatoceles are cystlike rarefactions that develop within the lung parenchyma. They are unusual findings and, when present, are very suggestive of staphylococcal pneumonia.[1-3] Pneumatoceles also have been reported to occur occasionally in pneumonias caused by *Escherichia coli*,[4] *Klebsiella pneumoniae*,[5] *Mycobacterium tuberculosis*,[6] *Haemophilus influenzae*,[7] and group A streptococci.[8]

Pneumatocele formation is thought to be rare in pneumococcal pneumonia. Standard pediatric textbooks mention effusion and empyema but not pneumatoceles as complications of this type of pneumonia.[9,10] We are aware of only two reports that describe a total of five children with pneumococcal pneumonia in whom pneumatocele formation occurred.[11,12] Recently, we encountered two infants with pneumococcal pneumonia and bacteremia; during their recovery, pulmonary pneumatoceles developed that were indistinguishable from those associated with staphylococcal pneumonia. Resolution in each case was complete and uncomplicated. The unusual association of pneumatoceles with pneumococcal pneumonia prompted us to report these two cases.

REPORT OF CASES

Case 1.—Four days before admission to the hospital, fever and a nasal discharge developed in a 14-month-old girl. The night before admission, she became irritable and was grunting, but there was no coughing or wheezing. Medical history was unremarkable, except for an episode of bronchiolitis that required hospitalization when the patient was 10 months old.

Results of a physical examination on admission disclosed a fairly well-developed girl in acute respiratory distress, with grunting, subcostal and intercostal retractions, and flaring of alae nasi. Other findings included the following: temperature, 40 °C; respirations, 60/min; and pulse, 160 beats per minute. The patient's mucous membranes were pale and congested. Auscultation of the lungs showed decreased breath sounds and rales over the right upper lung field. The results of the rest of the examination were unremarkable.

Laboratory studies disclosed the following values: hemoglobin, 7.8 g/dl; hematocrit, 26%; and leukocytes, 27,200/cu mm, with 62% segmented neutrophils, 28% band forms, 6% lymphocytes, and 4% monocytes. Peripheral smear showed toxic granulations of leukocytes and hypochromia and microcytosis of erythrocytes. Reticulocyte count was 1.2%, and results of a test for sickle hemoglobin were negative. A roentgenogram of the chest showed consolidation of the right upper lobe, with adjacent pleural thickening (Fig 1, left). A blood culture was obtained, and the patient was started on a regimen of intravenous (IV) ampicillin sodium (200 mg/kg/24 hr). On the same day, she was given a blood transfusion. Subsequently, the blood culture was noted to be positive for *Streptococcus pneumoniae*, and her antibiotic treatment was changed to IV aqueous penicillin G (200,000 units/kg/24 hr). On the fifth day of hospi-

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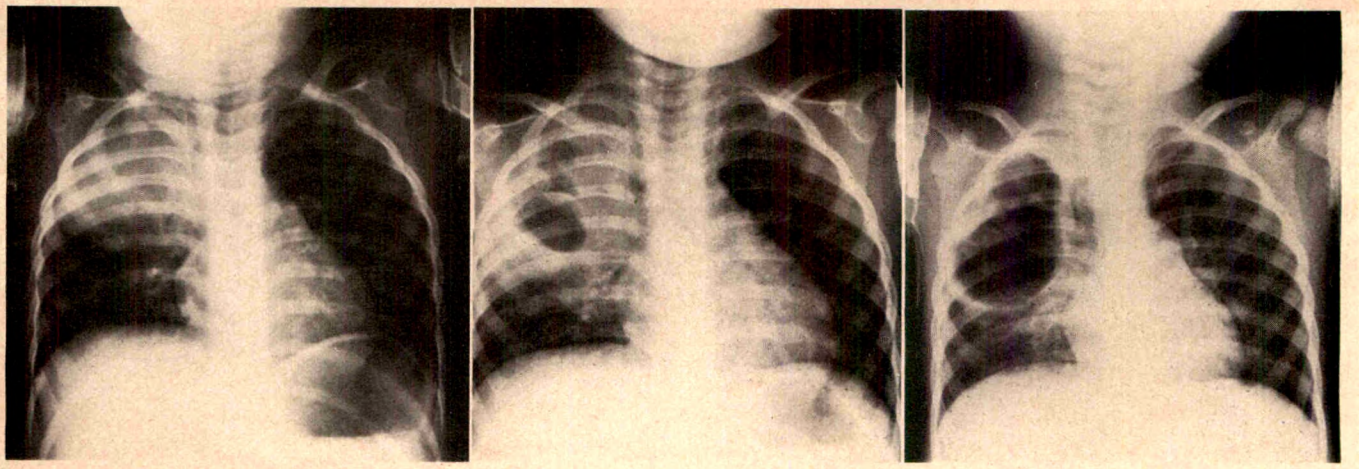


Fig 1.—Case 1. Left, Admission roentgenogram showing right upper lobe pneumonia. Center, Chest roentgenogram on day 5 showing radiolucency in pneumonic area. Right, Pneumatocele formation on day 7.

talization, the patient was still febrile. A chest roentgenogram done on the same day showed radiolucent areas within the pneumonic consolidation (Fig 1, center). On day 7, definite pneumatoceles were seen in the area of the resolving pneumonia (Fig 1, right). Meanwhile, the patient was improving clinically and she became afebrile on the eight hospital day. She received a ten-day course of IV antibiotics. Pneumatoceles were still present on the 12th day, when she was discharged. A follow-up roentgenogram 77 days after discharge showed complete resolution of the pneumatoceles.

CASE 2.—An 11-month-old girl was well until ten days before hospital admission when a cough, nasal discharge, and fever developed. She was given an oral decongestant during the five days before admission. On the day of admission, fever abated but the patient was noted to be grunting. Medical history was unremarkable.

Physical examination at the time of admission showed a well-developed infant in acute respiratory distress. She was grunting, and she had dry mucous membranes, intercostal retractions, and flaring alae nasi. Findings included the following: temperature, 38.6 °C; respirations, 56/min; and pulse, 164 beats per minute. Auscultation of the lungs showed decreased breath sounds over the right lung field. Abdominal examination showed the liver edge to be palpable 4 cm below the right costal margin. The results of the rest of the examination were unremarkable.

Laboratory studies disclosed the following values: hemoglobin, 6.6 g/dl; hematocrit, 18%; leukocytes, 2,300/cu mm, with 10% segmented neutrophils, 18% band forms, 71% lymphocytes, and 1% monocytes. Peripheral smear showed hypochromia and target cells. Reticulocyte count was 0.6% and hemoglobin electrophoresis revealed heterozygous state for hemoglobin S, with 2.8% fetal hemoglobin. A chest roentgenogram showed consolidation of the right upper and right middle lobes with a small effusion on the same side (Fig 2, left). A blood culture was obtained, and treatment with IV ampicillin sodium (200 mg/kg/24 hr) and methicillin sodium (200 mg/kg/24 hr) was started. On that same day the patient received a blood transfusion. Subsequently, *S pneumoniae* grew from blood culture, and her antibiotic treatment was changed to IV penicillin G sodium (200,000 units/kg/24 hr).

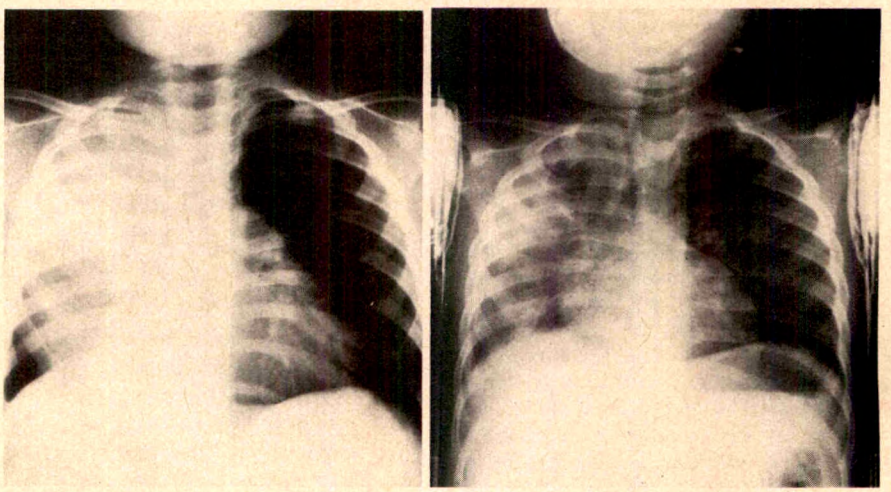


Fig 2.—Case 2. Left, Right upper and middle lobes infiltrates with pleural effusion on admission. Right, Progression to pneumatocele formation on day 9.

The patient's condition continued to improve gradually, and she became afebrile on the fourth hospital day. A repeated chest roentgenogram taken on the seventh day disclosed a radiolucent area within the pneumonic area in the right upper lobe. Therapy was changed to oral penicillin, and the patient continued to do well. A repeated chest roentgenogram on the ninth day showed further enlargement of the radiolucent area within the clearing pneumonic area in the right upper lobe (Fig 2, right). She received a 12-day course of antibiotics before she was discharged. A follow-up chest roentgenogram two weeks after discharge showed complete resolution of pneumonia and the pneumatocele.

COMMENT

Pneumatoceles have been reported in 16% to 61% of patients with staphylococcal pneumonia.[13,14] The majority of these patients were infants and children. In contrast, pneumococcal pneumonia in children has rarely been associated with pneumatocele formation.[11,12] In 1939, Benjamin and

Childe[11] reported their experience with 19 cases of "localized emphysematous air spaces" associated with pneumonia. Two of these cases occurred in 5- and 8-year-old children with pneumonia and pleural effusion. Pneumococci were cultured from the pleural fluid of the two patients. Pneumatoceles developed in both of them during their recovery phase. Causes of the remaining 17 cases were not determined. Ravitch and Fein[12] described 10,532 children with pneumonia admitted to the Harriet Lane Home, Baltimore, between 1932 and 1958. Among these patients, pneumatoceles developed in only three with pneumococcal pneumonia and empyema, but details were not available.

All of the reported five cases and our two patients had pleural involvement. This was in the form of effusion or pleural thickening on the same side of the lung where pneumonia was found.

More than one mechanism has been suggested to explain the development of these air cysts in the course of a pneumonic process. Caffey[15] proposed that pneumatoceles represent grossly distended bronchioles distal to an endobronchial check-valve, produced by inflammation and narrowing of a bronchus. Conway[16] believed that, in addition to a valvelike mechanism, a peribronchial abscess cavity is necessary. The cavity, which is interstitial in location, traps air and enlarges into an air cyst. With the resolution of inflammation, the check-valve mechanism subsides, and, with time, the pneumatoceles disappear. Recently, Boisset[6] presented data from postmortem specimens; he suggested that pneumatoceles are actually a form of subpleural emphysema. He claimed there were interlobular spaces containing "air corridors" linked to the subpleural cavity. He proposed that air from the respiratory tree escapes along these paths, accumulating beneath the pleura and forming large bullae.

Hemorrhagic necrosis,[10] suppuration into bronchial lumens, and destruction of bronchial walls tend to accompany staphylococcal pneumonia.[17] The absence of such intense suppurative response and the lack of bronchial wall necrosis may explain the rarity of pneumatocele formation in pneumococcal pneumonia.

On the basis of the roentgenographic findings and in the absence of positive blood cultures, our two cases could have been mistaken for staphylococcal pneumonia. For all cases of pneumonia, it is imperative that causative agents be sought for in the blood, pleural fluid, or, if necessary, lung tissue culture. Based on our present report and others in the literature,[1-8,11,12] it is evident that pneumonia with pneumatoceles, though very suggestive of staphylococcal infection, can be caused by several other bacterial agents, including pneumococci.

Nonproprietary Name and Trademarks of Drug

Ampicillin sodium—*Amcill-S, Omnipen-N, Penbritin-S, Polycillin-N, Principen/N.*

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Pneumococcal Empyema in Childhood

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• **Two serotypes, uncommon in pediatric infections, accounted for a disproportionately large number of cases of pneumococcal empyema at the Children's Hospital of Pittsburgh. Eight of ten empyemas were caused by types 1 or 3, and two additional cases of mixed infection involved the type 3 pneumococcus. The type 3 pneumococcal empyemas tended to be more severe than those due to other serotypes. Counterimmunoelectrophoresis (CIE) appeared to be more useful than culture in establishing the cause of this condition; in seven of ten cases, the pleural fluid was CIE positive while cultures of blood and pleural fluid were negative. In each of the seven culture-negative cases, antibiotics had been given prior to hospitalization. One case of type 7 pneumococcal empyema illustrated the potential value of the Ouchterlony test for the etiologic diagnosis of this condition.**

(*Am J Dis Child* 132:1094-1096, 1978)

A recent review of serotypically defined infections due to *Streptococcus pneumoniae* at Children's Hospital of Pittsburgh suggested that pneumococcal pneumonia with pleural involvement was often due to two serotypes that are seldom isolated from infections in children.[1] The etiology of some of these infections was established solely by counterimmunoelectrophoresis (CIE). The purposes of this study were therefore to evaluate evidence of type specificity for pneumococcal empyema of childhood and to compare the diagnostic usefulness of CIE and culture for this condition.

METHODS

Hospital records were reviewed for January 1972 through March 1978. Ten cases of pneumococcal empyema were verified by thoracentesis and isolation of bacteria from pleural fluid or blood, or by demonstration of polysaccharide capsular antigens in pleural fluid or concentrated urine by CIE.[1,2] The CIE procedure, initiated at this hospital in January 1975, employs equipment originally designed for detection of hepatitis B antigen (Aus-test Counterelectrophoresis test system, Abbott Laboratories, North Chicago), pneumococcal antisera from Statens Serum-institut, Copenhagen, Denmark, and *Haemophilus influenzae* type b antiserum from Hyland Laboratories, Costa Mesa, Calif. Clinical specimens were initially screened with pneumococcal antiserum pools A through F and omniserum containing antisera for 83 pneumococcal serotypes. Pneumococcal antiserum pool H was also employed after the first few months of 1975. If pneumococcal antigen was detected with the pools, typing was performed with monospecific antisera. Respiratory secretions were not tested for bacterial antigens.[3,4] Serotyping of isolates was performed at this hospital by either quellung reaction or CIE.

Since complete description of the fluid obtained at thoracentesis was not recorded on the medical record in all cases, empyema was defined for this study as pleural infection with a moderate to massive amount of fluid demonstrated by roentgenographic examination, and bacteria or bacterial antigens present in the pleural fluid or blood. Four children with pneumococcal pneumonia and small amounts of pleural fluid were therefore excluded; the pneumococci responsible were type 1, two cases; type 4, one case; and a strain from one case that was not typed. Also excluded were two children with mixed infection (both involving type 3 pneumococcus) and three with empyema due to *H influenzae* type b (all three CIE positive but culture negative with prior antibiotic treatment). A total of 36 pleural fluid specimens were tested by CIE between January 1975 and March 1978, and bacterial antigens were detected in 14 (11 *S pneumoniae* and three *H influenzae* type b).

RESULTS

The Table summarizes features of the ten cases of pneumococcal empyema, eight of which were due to types 1 or 3. In three cases, *S pneumoniae* was isolated from blood, pleural fluid, or both. For the seven others, the etiology was determined by CIE alone because both blood and pleural fluid cultures were negative; antibiotics had been given prior to hospitalization and culture in each case. Capsular antigens were found in all eight pleural fluids tested, in two of six concen-

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Selected Characteristics of Patients With Pneumococcal Empyema at Children's Hospital of Pittsburgh, From January 1972 Through March 1978

Date	Age, yr	Prior Antibiotics	Culture		Counter-Immunoelectrophoresis			Duration of Hospitalization, Days
			Blood	Pleural Fluid	Blood	Pleural Fluid	Urine	
1/72	4	No	+*	1†	NT‡	NT	NT	15
1/75§	4	Yes	0	0	0	1	1	10
3/75§	11	Yes	0	0	0	1	0	7
11/75	11	Yes	0	0	NT	1	1	14
12/75	3	Yes	0	0	0	1	0	31
3/77	5	No	7	0	NT	NT	NT	13
3/77	7	Yes	0	0	NT	3	0	19
3/77	3	No	0	3	NT	3	NT	32
4/77	8	Yes	0	0	0	3	NT	28
3/78	2	Yes	0	0	0	7	0	16

*Pneumococcus isolated but not typed.
†Pneumococcal serotype.
‡Not tested.
§Previously reported.[2]

trated urine samples, but in none of five serum samples. All CIE-positive pleural fluids reacted with both omniserum and one of the seven pneumococcal antiserum pools. The Ouchterlony[5] technique of double immunodiffusion in agar was used to confirm the presence of type 7 antigen in one pleural fluid that was CIE positive only after overnight incubation in the refrigerator. A 40-fold dilution of this pleural fluid was still Ouchterlony positive and an 80-fold dilution was negative.

Noninfectious underlying disease was found in only one child with empyema (Down's syndrome), but one other child had varicella and four others had rhinitis at the onset of their illnesses. All patients recovered completely with various combinations of therapy with penicillin, thoracentesis, and chest tube drainage. The mean duration of hospitalization for those with empyema due to type 3 pneumococcus was nearly twice that for empyema due to other pneumococcal serotypes (26.3 vs 15.1 days).

COMMENT

The unusual distribution of pneumococcal serotypes in this group of children with empyema is unexplained. Most pneumococcal empyemas were found to be due to either type 1 or type 3, whereas 19 different serotypes were responsible for other kinds of pneumococcal infection at this hospital during the same period.[1] The methods used for the identification of bacteria are not a likely cause of the predominance of these two serotypes in empyema fluid, since the same methods were used for all kinds of pneumococcal infection. A recent report from Thailand demonstrated that type 5 pneumococcal antigen may be commonly found in pleural fluid of children undergoing thoracentesis in that country,[6] but an association of pneumococcus types 1 and 3 with empyema has been reported from Denmark[7] and the United States.[8] Although neither serotype is commonly found in childhood infections,[9] types 1 and 3 were both included among serotypes reported to have been isolated recently from children with sickle hemoglobinopathy.[10] Type 3 pneumococcus also commonly occurs in older persons, characteristically producing serious infections with a high mortality.[8,11,12] The unusual severity of type 3 pneumococcal infections may be related to the antiphagocytic properties of the organism's thick capsule.[13]

The tendency for longer hospitalization of Pittsburgh children with type 3 pneumococcal empyema, as compared to those with empyema due to other pneumococcal serotypes, is therefore not surprising. A possible explanation might be relative resistance to penicillin,[14] but type 3 has not been one of the serotypes implicated in the literature. Moreover, the single type 3 isolate in our series (Table) had a minimum inhibitory concentration (0.02 μg/ml) similar to that for most other pneumococcal isolates tested at this hospital during the past six months. (A study of more than 100 strains of *S pneumoniae* from patients at this hospital between December 1977 and June 1978 has yielded two with relative insensitivity to penicillin.)

Our two mixed pleuropulmonary infections (not included in the Table) both involved the type 3 pneumococcus, one with coagulase-positive *Staphylococcus* and the other with *H influenzae* type b. It is of interest that a recent report on the use of CIE in the diagnosis of empyema included a mixed infection with *S pneumoniae* and *H influenzae* in an adult.[15] Others have rarely encountered either of these two organisms in mixed pleural infections.[16]

The results of our survey suggest that CIE may be even more useful than culture in the etiologic diagnosis of pneumococcal empyema in childhood, probably because of frequent prior antibiotic therapy. Rapid sterilization can occur with exposure of pneumococci to even low concentrations of antibiotics, but capsular antigens are still detectable by CIE and by the double immunodiffusion test of Ouchterlony if abundant numbers of organisms were originally present.

Types 7 and 14 pneumococci are reported to be common causes of pediatric infection,[9] but may not be detected by CIE unless a special buffer[17] is employed; the capsular antigens of these two serotypes are positively charged in most buffer systems, whereas the antigens of other pneumococcal serotypes are negatively charged. Counterimmunoelectrophoresis depends on antigen with a negative electrical charge and antibody with a positive charge. The Ouchterlony test is neither as rapid nor as sensitive as CIE, but it does not depend on electrical charge of the reactants. We have previously found this test to be valuable in identifying types 7 and 14 pneumococcal isolates that could not be serotyped by CIE.[1] The fact that one empyema fluid was Ouchterlony positive, even after considerable dilution, suggests that this simple test may be sufficiently sensi-

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tive to be helpful in the etiologic diagnosis of pneumococcal empyema, particularly where cultures and CIE are negative.

Despite their advantages, CIE and Ouchterlony tests are not available in many hospital laboratories. The cost of potent and specific antisera has probably slowed general acceptance of CIE. Latex particle agglutination appears to have the advantages of simplicity, lower cost, and greater sensitivity when used for the detection of *H influenzae* type b capsular antigen,[18] but there are no published reports of systematic study of pleural fluid for pneumococcal antigens with latex particle agglutination. Moreover, it is possible that most empyema fluids contain high concentrations of bacterial antigens,[15] and that more sensitive methods would not yield substantially better results. In this regard, CIE with omniserum was able to detect pneumococcal antigen in all our pleural fluids that reacted with the higher-titer antiserum pools. Our results for one pleural fluid with the Ouchterlony test are also consistent with this thesis.

Lack of specificity is a potential problem with any immunologic test for bacterial capsular antigens because cross-reactions can occur.[19] Reports in the literature, however, have indicated that cross-reactions are rarely seen when CIE is used for the etiologic diagnosis of empyema.[6,15] Our more than three years' experience with this test in a clinical laboratory demonstrates that distinct lines of precipitation in agar with CIE have a high degree of specificity. In tests of pleural fluid, spinal fluid, joint fluid, serum, and concentrated urine during this period, we have observed no cross-reactions between different pneumococcal serotypes or between pneumococci and other bacteria.

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Recurrent Reye's Syndrome

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• **The clinical diagnosis of recurrent Reye's syndrome can be made only after a systemic exclusion of other diagnostic possibilities. We report such a case, providing guidelines for a complete clinical and biochemical evaluation of this entity. If a comprehensive study of patients experiencing recurrent Reye's syndrome is to be made, each patient must be subjected to thorough examination.**

(*Am J Dis Child* 132:1097-1099, 1978)

Since the initial description by Reye et al[1] of an acute encephalopathy associated with fatty degeneration of the liver, many reports have appeared further defining this clinical entity. A number of biochemical abnormalities have been described in patients with Reye's syndrome. These include hyperammonemia,[2] hyperaminoacidemia,[3] short-chain fatty acidemia,[4] a variable organic aciduria,[5,6] and abnormal muscle enzymes,[7] all of which may possibly contribute to the disease process. Nevertheless, a full understanding of the etiology, pathogenesis and optimal treatment of Reye's syndrome has not been attained. Meanwhile, the spectrum of this disorder grows continually wider as the diagnosis is being suspected with increasing frequency.

A recent report[8] suggests that Reye's syndrome can be recurrent. However, numerous disease states may produce encephalopathy, elevation of serum transaminase levels, and other signs of liver dysfunction resembling Reye's syndrome. Such diseases include salicylate, chlordane, and disulfiram intoxication; influenzal and varicella encephalitis; Jamaican vomiting sickness[9]; hypovolemic shock[9]; genetically transmitted ornithine transcarbamylase deficiency[10]; systemic[11,12] or muscle[13] carnitine deficiency; and inborn errors of organic acid metabolism, eg, glutaric aciduria.[14]

Before the diagnosis of recurrent Reye's syndrome can be made, these other diagnostic possibilities must be eliminated. This requires elicitation in the history of foreign travel and of possible chlordane or disulfiram exposure, a toxicology analysis for salicylates, appropriate viral cultures, assessment of possible hypovolemic shock, and an evaluation for aminoaciduria or organic aciduria, along with later diagnostic studies to evaluate possible ornithine transcarbamylase deficiency or systemic carnitine deficiency.

We report a case of recurrent Reye's syndrome where a complete clinical workup of this entity has been accomplished. Included is the first discussion of a systematic evaluation of known biochemical lesions that simulate this disorder, may be amenable to more specific therapy, and must be excluded from the differential diagnosis.

REPORT OF A CASE

First Admission.—The patient was a 13-year-old girl in good health with no history of foreign travel or of chlordane or antabuse exposure. Three days before admission, symptoms of a flu-like illness occurred in the context of an influenza B epidemic in the community (personal communication, University of Colorado Medical Center, Virology Laboratory). Pernicious vomiting began the next day. Subsequently, she became increasingly lethargic and sleepy. Irritability and belligerent behavior prompted her admission to the Denver Children's Hospital on Feb 2, 1976.

On admission, the patient was disoriented and combative. Her temperature was 36.4 °C; pulse rate, 100 beats per minute; respirations, 40/min; and blood pressure, 122/80 mm Hg. Positive physical findings included a palpable liver 3 cm below the costal margin at the right midclavicular line and generalized hyperreflexia with clonus. An extensor plantar response was present on the right. The CSF was within normal limits. Toxicology analysis was positive for small amounts of salicylates in the urine (15 mg/dl). The creatinine phosphokinase level was 52 IU/liter (normal, 5 to 30 IU/liter). Serum glucose values remained normal throughout her course. Other chemistry data are presented in the Table. Her condition was diagnosed clinically as Reye's syndrome, and treatment was begun with fluid restriction, intravenous hypertonic glucose solutions, neomycin sulfate, and dexamethasone.

Despite these measures she became progressively obtunded, and on the second hospital day she was in stage II coma,[15] with continued laboratory evidence of hepatic dysfunction. An EEG demonstrated grade II activity.[16] Fifty-four hours after admission the patient's clinical condition began to improve. By 68 hours she was fully alert and was taking oral fluids. Ther-

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Clinical Stage and Laboratory Values							
Day of Admission	Clinical Stage[15]	Serum Ammonia,* μg/dl	SGOT, IU/ml	Alkaline Phosphatase, IU/ml	Lactic Dehydrogenase, IU/ml	Total Serum Bilirubin, mg/dl	Prothrombin Time, sec, Patient/Control
First admission							
1	I to II	198	108	226	255	1.0	14.8/11.8
2	II to III	168	226	239	321	1.3	11.5/11.0
3	III to 0	159	112	...	234	...	...
4	0	...	132	...	191	...	...
5	0	...	...	...	...	1.6	...
6	0	...	26	181	110	0.8	10.5/12.5
Second admission							
1	I to III	230	85	92	168	1.5	12.5/11.0
2	III	196	310	92	410	...	...
3	III to 0	81	405	94	396	1.5	11.5/12.5
4	0	96	518	106	353	...	...
5	0	150	220	108	133	1.2	...
6	0	20	45	...	66	...	...

*Normal value, less than 80 μg/dl.

apy was discontinued. She remained afebrile throughout her hospital course. Thereafter she made an uneventful recovery and was discharged on the sixth hospital day without evidence of neurologic sequelae. Viral cultures returned later were negative.

Second Admission.—The patient was in good health during the next year, and findings from an interim examination were unremarkable. Her performance in school was above average and unchanged.

Six days before her second admission, without recent foreign travel or exposure to chlordane or disulfiram, she experienced the onset of a flu-like illness. An influenza B epidemic was once again present in the community (personal communication, University of Colorado Medical Center, Virology Laboratory), with many classmates and both of her siblings ill with similar symptoms. However, while the siblings showed a progressive recovery, the patient's condition deteriorated, with the onset of pernicious vomiting on the third day of her illness. On the fifth day, she became irritable and belligerent and was hospitalized. She underwent intravenous hydration overnight after normal complete blood cell count and serum electrolyte values had been obtained. The next morning the finding of an SGOT level of 126 IU/ml with little change in her clinical status prompted a transfer to Denver Children's Hospital on Feb 14, 1977.

In the receiving unit her irritability progressed to combativeness, and she had to be restrained. Her temperature was 37.2 °C; pulse rate, 80 beats per minute; respirations, 24/min; and blood pressure, 115/80 mm Hg. The liver was palpable 1 cm below the right costal margin at the midclavicular line. Her pupils were dilated and reacted only sluggishly to light. She was hyperreflexic. Toxicology analysis showed 10 mg/dl of salicylates in her urine. The serum glucose level was 105 mg/dl and remained in the normal range during her hospital course. Other laboratory data are recorded in the Table.

Within one hour of admission she became delirious, then unresponsive. The pupils were fully dilated and reacted only minimally to light. Generalized clonus was elicitable. A Babinski's sign was present on the right. In conjunction with these clinical findings, an abnormal liver profile (Table), including a serum ammonia level of 230 μg/dl, suggested the diagnosis of Reye's syndrome. Treatment was begun with fluid restriction, neomycin sulfate, and glycerin. On the second hospital day an EEG showed grade II changes.[16] She remained in stage II coma[15] for 27 hours, when her condition rapidly improved. By the third hospital day she appeared well, and therapy was discontinued. There was no fever or rash during her hospital course. No residual signs were noted. Liver enzyme and serum ammonia levels returned to normal, and the patient was discharged on the sixth hospital day. Viral cultures later grew only *Herpesvirus hominus* from a throat swab. After this second episode of illness the patient required a prolonged convalescence of eight months before she felt recovered. Even then, generalized weakness persisted for a full year. Her school achievement, while remaining above average, clearly declined from past performance.

SPECIAL STUDIES

The patient was tested for partial deficiency of ornithine transcarbamylase by measurement of urinary orotic acid levels after a meal of protein, 1 g/kg of body weight, as described by Goldstein et al.[17] Serial urine specimens collected at 0-time and every two hours after ingestion of the test meal revealed no measurable orotic acid, suggesting normal function of ornithine transcarbamylase.

Urine organic acid levels, measured by gas chromatography-mass spectrometry using separation techniques previously described,[18] demonstrated no detectable abnormality in the fasting or fed state.

Plasma carnitine level, measured after the patient had recovered, by the method of Karpati et al,[11] was 29.2 nmole/ml, with normal values ranging from 27.9 to 67.2 nmole/ml.

COMMENT

The similarity, in most aspects, of this patient's initial and recurrent episodes of Reye's syndrome is striking. Almost exactly one year apart, during influenza B epidemics, flu-like symptoms developed associated with pernicious vomiting preceding an acute encephalopathy, which prompted hospital admission. The history, physical findings, and laboratory data are consistent with the clinical definition of influenza B-associated Reye's syndrome as established by Corey et al[19] after their review of 379 cases. While the therapeutic intervention differed somewhat, both hospital courses were similar, with the patient showing increasing evidence of encephalopathy for 54 hours on the first admission and 30 hours on the second admission before undergoing a rapid and uneventful recovery.

Although Reye's syndrome was initially described by its postmortem

pathologic features, increasing experience has provided histologic confirmation of clinically diagnosed cases.[19-23] The need for hepatic tissue specimens to confirm the diagnosis of Reye's syndrome remains controversial. A liver biopsy continues to be indicated when there are deviations from the typical clinical profile; however, the reports by Corey et al[19] and others[20-23] have made the syndrome a definable clinical entity.

The precise nature of Reye's syndrome remains undefined. Present evidence suggests that it may be the result of acute mitochondrial dysfunction as the final common pathway from many causes.[24] Hepatocyte mitochondria clearly are abnormal. Structurally, they exhibit varying degrees of enlargement, a decrease in matrix density, and loss of dense bodies.[24] Biochemically, there is an associated decrease in urea cycle enzyme activity,[2-26] abnormal short-chain fatty acid metabolism,[4] and inefficient mobilization and excretion of amino acids,[3] with the possibility of altered metabolism of exogenous or endogenous toxins.[6,27,28] Perhaps some of these metabolic events act synergistically to create the devastating clinical course seen in many patients.

Of these various biochemical aberrations, the urea cycle enzyme deficiencies that are associated with the hyperammonemia seen in Reye's syndrome have been most widely studied. Independent investigations have accumulated evidence that tissue ornithine transcarbamylase in liver is usually transiently diminished in the syndrome and that carbamyl phosphate synthetase is reduced in about half of the patients.[25,26] Abnormal kinetics for ornithine transcarbamylase has been offered as evidence for possible genetic ornithine transcarbamylase variants making some children susceptible to Reye's syndrome during a viral illness.[10] This has not been confirmed by other investigators.[29] In our patient, ornithine transcarbamylase was shown not to be genetically deficient based on response to a protein load. The family history was also negative for perinatal or infant deaths in males or protein intolerance in females.[30,31]

A new masquerader of recurrent Reye's syndrome has recently been described due to carnitine deficiencies.[11-13] Obvious muscle weakness need not be present to consider the diagnosis.[12,13] Plasma carnitine levels were normal in our patient, ruling out systemic carnitine deficiency. As she had attained adolescence without myopathic symptoms, a muscle biopsy was not performed.

To our knowledge this is the first report of a case of recurrent Reye's syndrome where other diagnostic possibilities have been considered and eliminated. When histopathology is not available in making the diagnosis of recurrent Reye's syndrome, other diagnoses must be excluded. This would necessarily include the systematic exclusion of foreign travel, toxic ingestions, certain viral encephalitides, hypovolemic shock, the female carrier state for ornithine transcarbamylase deficiency, and systemic carnitine deficiency. Only then can patients with recurrent Reye's syndrome be adequately identified and study of this unusual susceptibility be undertaken.

Andrew G. Engel, MD, the Mayo Clinic, Rochester, Minn, performed the serum carnitine determination.

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Developmental and Psychoeducational Sequelae of Chronic Otitis Media

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• **The developmental, psychological, and educational sequelae of chronic otitis media occurring during the first three years of life were investigated in a selected group of children with educational difficulties. One group of children had a history of chronic and severe otitis media, requiring myringotomy after 3 years of age. The control group had infrequent and relatively mild episodes of otitis media and no surgical intervention. Children with chronic and severe otitis media manifested substantial delays in speech and language, auditory processing deficits, disturbances in auditory-visual integration, reading disorders, and poor spelling skills. Early medical and educational intervention for children with a high-risk profile of language delay and severe chronic otitis media is suggested as a possible strategy for preventing the development of a specific learning disability.**

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Purulent and serous otitis media occur most frequently in children under 10 years of age.[1] Transient and permanent impairment of auditory acuity of varying degrees has been observed as a complication of chronic otitis media.[2-4] Chronic middle ear disease may have an additional significance when it occurs before age 4 years, during the critical periods of speech and language development.[5,6] Intermittent hearing loss and distortion of auditory signals during the early years of language acquisition may be associated with the development of auditory processing disturbances and subsequent deficiencies in academic performance. It is hypothesized that developmental, psychological, and educational delays in some school-age children may represent the residual complications of chronic middle ear disease incurred during early childhood.

Central auditory processing disturbances are included under the category of "specific learning disabilities" and encompass impairments of attention, sequential memory, discrimination, sound blending, and closure skills.[7,8] Although the child's cognitive functions may remain intact, the processing of auditory input is deficient. Frequently, disturbances in central auditory processing interfere with the ability to develop reading, spelling, and mathematical proficiency, despite average or above-average intelligence.[9-11]

Chronic otitis media in early childhood has been associated with delays in the acquisition of language skills.[12,13] Impaired intellectual development[14,15] and educational difficulties[16,17] have likewise been reported to be complications of chronic otitis media occurring during the language formative period, from birth to 3 years of age.

The present investigation was designed to delineate the pattern of auditory processing deficits in a select group of children with suspected academic problems and associated histories of chronic otitis media occurring during the first three years of life. The patterns obtained from a comprehensive evaluation were compared with the test performances of a similar group of children who experienced relatively mild episodes of otitis media during the same life period. The comparative analysis was used in an attempt to define a high-risk profile, unique to children with early and severe otitis media and academic underachievement. In addition, a critical variable was explored: Do children

with early and severe otitis media experience a true general intellectual impairment, or is the appearance of intellectual decline secondary to specific auditory processing deficits?

SUBJECTS AND METHODS

Subjects

Forty subjects were included in this study, ranging in age from 6 to 11 years. All of the children were referred for a multidisciplinary examination because of a chief complaint of academic underachievement of undetermined etiology and severity. Comprehensive interdisciplinary evaluations were performed by the staff of the Section of Developmental and Behavioral Pediatrics, Department of Pediatrics, University of Tennessee Center for the Health Sciences, Memphis. All children included in the investigation were required to satisfy several criteria:

1. All children were from white, middle-class socioeconomic backgrounds, as determined by family income, area of residence in the city, and the professional status of the working parent.

2. A confirmed history of otitis media during the first three years of life was required. Confirmation was established by two methods: (a) medical records obtained from each child's pediatrician and (b) parent interviews detailing the symptomatology, frequency, and severity of the episodes of middle ear disease. Only subjects representing extremes on the continuum of severity and frequency of the disease were utilized because of the variability in diagnostic procedures and clinical acumen in defining otitis media. One group with severe and frequent episodes of otitis media during the period from birth to 3 years of age was delineated. A second group had relatively mild episodes of the disease during the same age period. In an attempt to further differentiate relative severity of the disease, all subjects grouped as having severe otitis media were additionally required to have had myringotomy procedures, whereas children in the mild disease group did not.

3. Subjects with a history of suspected prenatal, perinatal, or postnatal CNS disease or injury were excluded from the study.

4. Subjects with severe behavioral or emotional disorders, as determined by psychological evaluation, were not included in the study.

5. Children with visual perceptual dysfunctions, as determined by multidisciplinary evaluation, were excluded from the investigation. This criterion enabled a primary focus on auditory processing and academic achievement as they relate to early otitis media.

6. To control for the factor of intelligence, which can influence performance on various achievement tests, only subjects with a full-scale IQ above −1 SD below the mean were utilized. This criterion established an IQ of 85 as the minimum score for inclusion in the study.

All of the children were evaluated by comprehensive medical, neurological, psychological, audiological, and educational examinations. The examiner responsible for each evaluation was not informed of the details of the child's history of otitis media. The children were assigned to one of two groups, based on the history of severity and subsequent surgical intervention for middle ear disease.

Group 1.—The 18 children in this group (average age, 8.6 years; 13 boys, five girls) had a history of multiple episodes of otitis media during the first three years of life. Middle ear disease included chronic serous otitis media and recurrent episodes of acute otitis media, documented by records obtained from pediatricians who cared for the child during the illness. Physical examination at the time of the office visit was the primary method of diagnosis. In addition, parent interviews confirmed the chronic nature of the illness, requiring extensive periods of antibiotic therapy and multiple visits to the pediatrician's office. In all instances, the reports from the pediatricians and parents described the otitis media as "almost continuous" during the three-year period. All of the children in group 1 had myringotomies performed between the ages of 3 and 5 years. Nine pediatricians provided medical care for the 18 subjects in this group; two physicians served seven of the children. Pure tone audiometry at the time of the current study indicated that seven of the children had a bilateral hearing loss of 10 to 20 dB (International Standards Organization [ISO]-1964), six had a unilateral hearing loss of 10 to 20 dB (ISO-1964), and five exhibited auditory acuity within normal limits.

Table 1.—Categorization of Abilities Measured by Wechsler Subtests

Verbal Subtests
Information
Comprehension
Arithmetic
Similarities
Vocabulary
Digit span
Measured Ability
General fund of knowledge
Analytical reasoning
Mental arithmetic
Concept formation
Expressive vocabulary
Auditory sequential memory
Performance Subtests
Picture completion
Picture arrangement
Block design
Object assembly
Coding
Visual attention to detail
Visual sequencing
Visual-spatial orientation
Visual reproduction of form
Visual-motor coordination

Group 2.—The 22 children in this group (average age, 8.3 years; 18 boys, four girls) had documented histories of relatively mild otitis media during the first three years of life, consisting of no more than one brief episode per year. Historical confirmation was obtained from medical records and reports from the child's pediatrician. In addition, parent interviews did not indicate the presence of persistent symptomatology associated with chronic middle ear disease. Ten pediatricians provided health care for the 22 subjects in this group. One physician served five of the children, while three of the pediatricians cared for three children each. Medical evaluation did not suggest the need for surgical intervention. Pure tone audiometry performed at the time of the current study indicated normal auditory acuity in 20 of the 22 subjects. Two of the children exhibited a bilateral hearing loss of 10 to 20 dB (ISO-1964) at the time of this evaluation.

Method

The multidimensional investigation included (1) a developmental assessment to determine the age of acquisition of motor, speech, and language skills; (2) psychological testing to assess verbal and nonverbal abilities; and (3) educational determinations of word recognition (decoding), spelling, and arithmetic skills.

Information regarding the child's age of acquisition of developmental skills was based on parent interviews and/or review of medical records without prior knowledge of the history of otitis media. Only patients whose developmental histories could be verified by written records (eg, a "baby book") were utilized, inasmuch as retrospective data are of questionable reliability and must be interpreted with caution.

The Wechsler Intelligence Scale for Children—Revised was used to assess verbal and nonverbal skills, as well as general intelligence.[18] The two doctoral-level clinical psychologists who administered the tests were unaware of the history of otitis media prior to the evaluation. Analysis included individual subtest performances of varying complexity measuring verbal, nonverbal, and auditory processing skills

Table 2.—Age at Acquisition of Developmental Skills

	Age, mo (Mean ± SD)	
	Severe Otitis Media (N = 18)	Mild Otitis Media (N = 22)
Walking	12.1 ± 1.1	11.4 ± 0.9
Speech		
Words*	18.0 ± 2.2	13.1 ± 1.6
Sentences*	34.1 ± 4.1	23.2 ± 2.0

*Tests for group differences significant at .05 level.

(Table 1). Children in both groups were compared with each other, as well as with norms from the general population. The pattern of performance was analyzed for evidence of auditory and visual processing deficits.

The Wide-Range Achievement Test[18] was used to evaluate educational performance in the areas of word recognition (decoding), spelling, and arithmetic. The examiners were unaware of the child's medical history. The pattern of errors as related to either auditory or visual perceptual deficiencies was assessed by a special educator. Since achievement levels vary according to age and intelligence, test performance in each academic area was compared with an expected achievement level based on the subject's age and intellectual ability.[19]

RESULTS

Speech and Language Development

Groups 1 and 2 were compared as to the age of attaining competence in language and motor development (Table 2). Analysis of variance statistical procedures indicated no significant difference in the age of developing walking skills between the two groups. However, significant differences ($P < .05$) were observed in the acquisition of (1) a four- to ten-word vocabulary and (2) the ability to formulate and utilize sentences of three or more words. Results indicate that children with severe chronic otitis media and surgical intervention were delayed in the major areas of speech and language development, as compared to the children in the mild otitis media group.

Intelligence Testing

A comparative analysis of intelligence levels between the two groups was performed (Table 3). Analysis of variance statistical procedures indicated a significantly ($P < .05$) poorer performance by children with a history of severe otitis media (group 1) on measures of overall intelligence (full-scale IQ), verbal intelligence (verbal IQ), and nonverbal intelligence (performance IQ). The results suggest a general intellectual deficit among the children with severe otitis media. Analysis of the individual subtest performances on the verbal and nonverbal sections was used to determine the relative contribution of each subtest to the total intelligence test profile. The observation of significant subtest scatter supports an argument in favor of selective deficits contributing to the lower IQ score, rather than a pervasive depression of intellectual ability.

Analysis of Deficits

A comparison of verbal subtest performance between the two groups is summarized in Fig 1. A scaled score of 10 on each subtest is average for the normal population. Results indicate that the group with severe otitis media performed significantly ($P < .05$) more poorly on tests that depend heavily on auditory processing skills (mental arithmetic and auditory sequential memory) and auditory association (concept formation). Groups 1 and 2 did not differ significantly on the more stable tests of intellectual ability such as general fund of knowledge and expressive vocabulary. In addition, the groups did not differ significantly on the test of analytical reasoning.

The mental arithmetic and auditory sequential memory subtests involve increasing complexity of auditory input. The subject must process each part of the question in order to perform adequately. On the other hand, the expressive vocabulary subtest requires the subject to respond to single-word input and therefore does not heavily tax auditory processing skills. General fund of knowledge and analytical reasoning subtest questions are lengthy but may be repeated and do not require the processing of each word in the question to obtain a correct response. Auditory processing

Table 3.—Intelligence Testing: Wechsler Intelligence Scale for Children

	IQ (Mean ± SD)	
	Severe Otitis Media (N = 18)	Mild Otitis Media (N = 22)
Full-scale*	100.6 ± 6.31	108.1 ± 5.26
Verbal*	99.1 ± 4.28	107.5 ± 5.36
Performance*	101.9 ± 7.27	109.1 ± 4.28

*Tests for group differences significant at .05 level.

may be a factor contributing to performance on these subtests, but it is not as critical as on the mental arithmetic and auditory sequential memory tests.

The differences in performance on nonverbal subtests are summarized in Fig 2. Results indicate significant ($P < .05$) subtest differences on those visual processing tests that depend on auditory processing and language skills. The visual sequencing test requires that the subject construct a story in sequence, using pictures. The visual-motor coordination test involves auditory-visual integration as well as fine-motor ability. Pure visual processing tests (visual attention to detail, visual-spatial orientation, and visual reproduction of form) were performed adequately by children in both the severe and mild otitis media groups.

Academic Skills

The relationship between reading level and intelligence was assessed. The correlation between full-scale IQ and reading level was 0.28, which was not statistically significant ($P > .20$). Intelligence did not appear to be the critical variable in determining reading level.

Expected achievement levels in word recognition (decoding), spelling, and arithmetic were obtained from achievement test norms. The subject's actual performance in these areas was compared with his expected achievement level. A mean discrepancy score for each group was obtained for the three academic areas (Table 4). The children in group 1 with a history of severe, chronic otitis media were significantly deficient ($P < .05$) in word

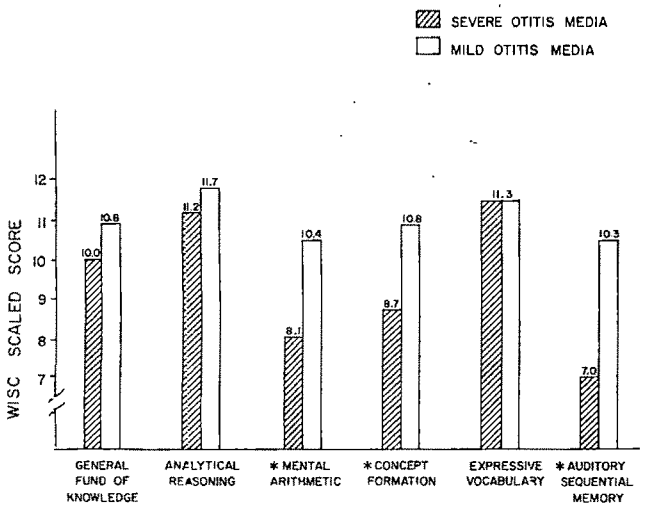


Fig 1 —Comparison of verbal test performances of severe vs mild otitis media groups, indicating deficits on subtests heavily dependent on auditory processing skills. Asterisk indicates group difference significant at .05 level.

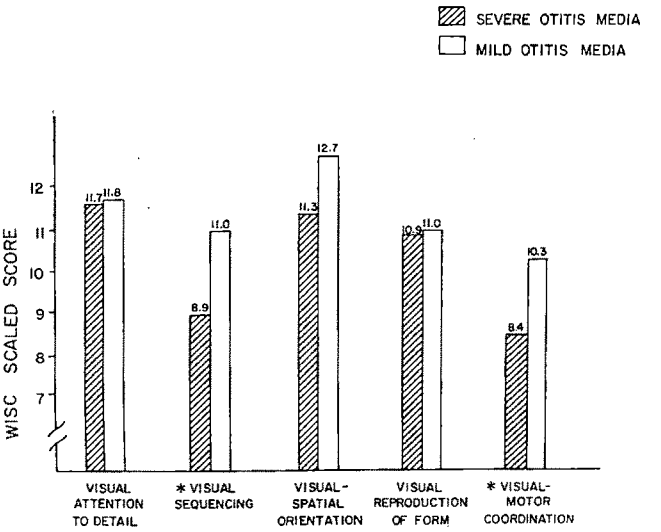


Fig 2.—Comparison of visual test performances of severe vs mild otitis media groups, indicating deficits on subtests combining auditory and visual processing skills. Asterisk indicates group difference significant at .05 level.

decoding and spelling skills as compared to children who had experienced mild otitis media. However, no difference was noted in arithmetic computation skills between the groups. It should be noted that the mean discrepancies for both groups were below grade level.

All subjects were referred for suspected academic difficulties, but, in some cases, the actual test performance in word recognition, spelling, and arithmetic was equivalent to or above the expected achievement level. This occurred in 13 of the 22 subjects with mild otitis media, but only three of the 18 subjects with severe otitis media showed a similar pattern. Children with a history of severe otitis media demonstrated a significantly greater ($P < .05$) deficit in word decoding and spelling skills.

Table 4.—Achievement Levels in Reading, Spelling, and Arithmetic

	Deviation From Expected Grade Level* (Mean ± SD)	
	Severe Otitis Media (N = 18)	Mild Otitis Media (N = 22)
Reading†	−2.1 ± 1.13	−0.8 ± 0.61
Spelling†	−2.0 ± 0.96	−0.9 ± 0.72
Arithmetic	−0.7 ± 0.94	−0.6 ± 0.63

*Based on chronological age and IQ.
†Tests for group differences significant at .05 level.

COMMENT

The results of this investigation suggest a possible association between delayed acquisition of speech and language, auditory processing disturbances, and early, severe otitis media in the children with the most severe educational handicaps. Transient hearing loss and distortion of auditory signals, due to middle ear disease during the critical periods of language and auditory processing development, may be an etiological factor. Significant developmental delays in word and sentence usage appear to be associated with chronic middle ear disease. The present investigation cannot resolve whether severe otitis media in the first three years of life is the sole determining factor in the development of subsequent auditory processing deficits. The disease process may well have continued past the age of 3 years, further complicating the development of adequate auditory processing skills. However, the profound delays in language development seen in the severe otitis media group are a significant finding. Early and severe chronic otitis media apparently contributed to a disruption of the maturational sequence in speech and language development.

In a study similar to the present investigation, Holm and Kunze[12] demonstrated language delays in children with early, severe otitis media. However, as noted by the investigators, variations in intellectual level were not controlled, a factor that could have influenced performance on speech and language tests. In the present study, intellectual abilities were controlled. Furthermore, the relationship between intelligence and reading was not significant ($P > .20$), suggesting the influence of other factors on reading levels, such as deficient auditory processing.

Previous studies indicated that impaired general intellectual function may be related to early and severe otitis media.[14,15] Results of the present investigation specifically differentiate the depression of particular skills that constitute the general intelligence scales. Children with severe, chronic otitis media exhibited deficits in specific verbal tasks that involve auditory processing, especially auditory sequential memory. The observed profile is similar to the characteristic pattern exhibited by learning-disabled children with specific auditory processing deficits.

In the present study, children with severe otitis media also experienced difficulty in performing tasks that required the integration of visual and auditory processing skills. Pure visual-

perceptual tasks were performed well if an additional auditory processing component was not superimposed. When this occurred, areas of normally intact visual perception were disrupted by the auditory perceptual deficit.

An association is suggested between early and severe, chronic otitis media and language deficiencies among children with academic underachievement. Severe, chronic otitis media during early childhood may be manifested as educational deficiencies in the school-age child. Although the middle ear disease may be resolved, the child's subsequent academic performance on tests of decoding skills (word recognition), spelling, and arithmetic may be impaired. Auditory processing deficits and disturbances in auditory-visual integration, in children with severe, chronic otitis media, appeared to be the major cause of their inadequate educational progress. Children with chronic otitis media performed poorly in word recognition and spelling skills, which are very dependent on intact auditory-visual coding and decoding skills.

Otitis media is a common disease of childhood; the cost of preschool speech and language, intelligence, and perceptual evaluations for all children with middle ear disease would be prohibitive. However, children specifically designated in a high-risk category for developing auditory processing deficits and educational difficulties require more intensive examination. A history of chronic otitis media in early childhood, in combination with a delay in acquisition of words and sentences, suggests the need for more comprehensive evaluation. The physician may be required to exercise more intensive medical intervention for children displaying this profile, including microscopic otoscopic examinations, pure tone and impedence audiometry, and developmental testing. In addition, children categorized as "high risk" because of speech and language delays may require surgical intervention, intensive speech and language stimulation, and specifically designed preschool programs.

Learning disabilities represent a heterogeneous group of disorders with diverse etiological backgrounds. Chronic otitis media is not presumed to be the sole factor causing all auditory processing deficits and subsequent learning disorders. The etiology of central auditory processing dysfunction cannot be defined in many cases. However, educational handicaps resulting from deficits in auditory processing, auditory-visual integration, and developmental language delays may be preventable in some children. A definable association between auditory processing disorders and chronic middle ear disease would be of significance in the prevention, detection, and therapy of specific types of learning disabilities. Longitudinal studies designed to further clarify the significance of the frequency and severity of middle ear disease, as it relates to language development and subsequent auditory processing skills, are needed. The results of the present investigation emphasize the need for a more in-depth understanding of the basic mechanisms of chronic otitis media, auditory processing disturbances, and resultant disorders of learning. A clarification of the proposed hypothesis that relates the three entities may provide clues for the prevention of specific learning disabilities.

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Dominant Inheritance of Scheuermann's Juvenile Kyphosis

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• **Familial occurrence of Scheuermann's juvenile kyphosis is well known, but no specific mode of inheritance has been recognized. We describe five families in which the disease seems to follow an autosomal dominant pattern of inheritance.**

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Scheuermann's juvenile kyphosis is an arcuate and fixed thoracic kyphosis developing around the time of puberty.[1] Its etiology and pathogenesis remain unknown, and a definite diagnosis is possible only by means of roentgenographic study. A familial tendency has been reported,[2,3] but no specific mode of inheritance was demonstrated.

We describe five families in which the disease seems to follow a dominant pattern of inheritance.

DIAGNOSTIC CRITERIA

Scheuermann's disease was originally defined as an abnormal and fixed thoracic kyphosis that develops around the time of puberty and is associated with wedge deformities of one or more vertebrae.[1] Sorensen's[2] diagnostic criterion was a kyphosis with at least three adjacent vertebrae, each with wedging of 5° or more. More recently, Bradford et al,[3] in their large series of Scheuermann's disease, made this diagnosis only in patients with kyphosis of more than 35°, with at least one vertebra with wedging of more than 5°. In our study, Bradford and colleagues' diagnostic criteria were present in at least one affected member of each family.

REPORT OF CASES

The roentgenographic findings are summarized in the Table, and the pedigrees illustrated in the Figure.

FAMILY A.—The proband (IV-8) was found to have Scheuermann's disease after a roentgenogram for a sports injury at the age of 17. However, his mother had noticed that his back was getting "round" at the age of 15. His siblings (IV-10 and IV-11) were also noticed by the parents to have a round back, especially in the sitting position. Subject IV-11 had the roentgenographic features of Scheuermann's disease although she is asymptomatic. Subject IV-10 did not have the roentgenographic features. The mother (III-2) was diagnosed as having Scheuermann's disease at the age of 15. She wore a brace for one year, did special exercises for another year, and

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Roentgenographic Findings								
				Wedging		Kyphosis		
Family	Pedigree	Age, yr	Degenerative Changes	Level	Degree	Degree	Apex	Scoliosis
A	III-2	46	T8-9	T-7	9	71	T-8	—
				T-8	8			
				T-9	5			
	IV-8	17	T6-9	T-8	5	47	T-9	—
	IV-10	16	None	None	None	37	T-8	—
	IV-11	12	T5-8	T-6	11	52	T-9	+
				T-7	8			
				T-8	5			
B	III-1	49	T6-8	T-7	11	50	T-7	—
				T-8	5			
	III-9	50	T6-8	T-6	7	52	T-7	—
				T-7	6			
				T-8	7			
				T-9	5			
	IV-1	21	T6-8	T-6	5	70	T-7-8	—
				T-7	15			
				T-8	14			
	IV-2	19	T6-9	T-7	4	47	T-7-8	—
				T-9	4			
	IV-3	18	T6-9	T-6	5	57	T-8	+
				T-7	9			
				T-8	7			
				T-9	5			
	IV-4	16	T6-9	T-7	10	45	T-8	—
				T-8	8			
				T-9	7			
	IV-5	14	T6-9	T-6	5	38	T-7	—
	IV-6	13	None	None	None	40	T-7	—
C*	III-8	47	L1-2	T-12	9	38	L-1	+
				L-1	16			
	IV-3	16	T-12	L-2	12	20	L-1-2	+
D	II-4	51	None	T-7	6	44	T-8	—
				T-8	7			
				T-9	8			
	IV-3	15	T6-9	T-7	5	50	T-8	—
				T-8	7			
				T-9	7			
E	III-5	37	T6-7	T-6	4	53	T-7-8	—
				T-7	7			
	IV-8	14	None	T-6	6	51	T-8	—
				T-7	6			
				T-8	7			
				T-9	7			

*The two cases in family C have a thoracolumbar kyphosis rather than thoracic. The changes seen are typical of those of Scheuermann's disease. Although in subject IV-3 the kyphosis is only 20°, it is thought that this is pathologic for this region and in fact represents a true Scheuermann's kyphosis.

has been complaining of mild to moderate back pain for the last ten years.

The maternal grandfather (II-6) was described by the mother as having a "round back" very noticeable in his later years. No other relatives were reported with "round backs."

Family B.—This family is very unusual, since both parents and all of their six children were affected. Subject IV-1 was diagnosed as having Scheuermann's disease during an annual check-up at the age of 16½ years. However, his parents had noticed his "bad posture" since his early teens. Shortly thereafter, the parents, sensitized by their oldest child's problem, asked to have their other children and themselves examined since they all had more or less of a "round back" deformity. All but one had Scheuermann's disease. The youngest (IV-6) had only a kyphosis of 40° with no wedging or degenerative changes. Neither parent (III-1 and III-9) had experienced any backaches or paid much attention to their own back deformity until their oldest child was found to have the disease. Their own parents, however, used to tell them and some of the maternal siblings (III-2, III-3, and III-5) to "straighten up" when they were in their teens. These siblings of the mother, and her father, were reported to have round backs, but were unavailable for examination.

Family C.—The proband (IV-3) was found to have Scheuermann's disease when he was investigated for a mild scoliosis. His father (III-8) was found to have the same deformity.

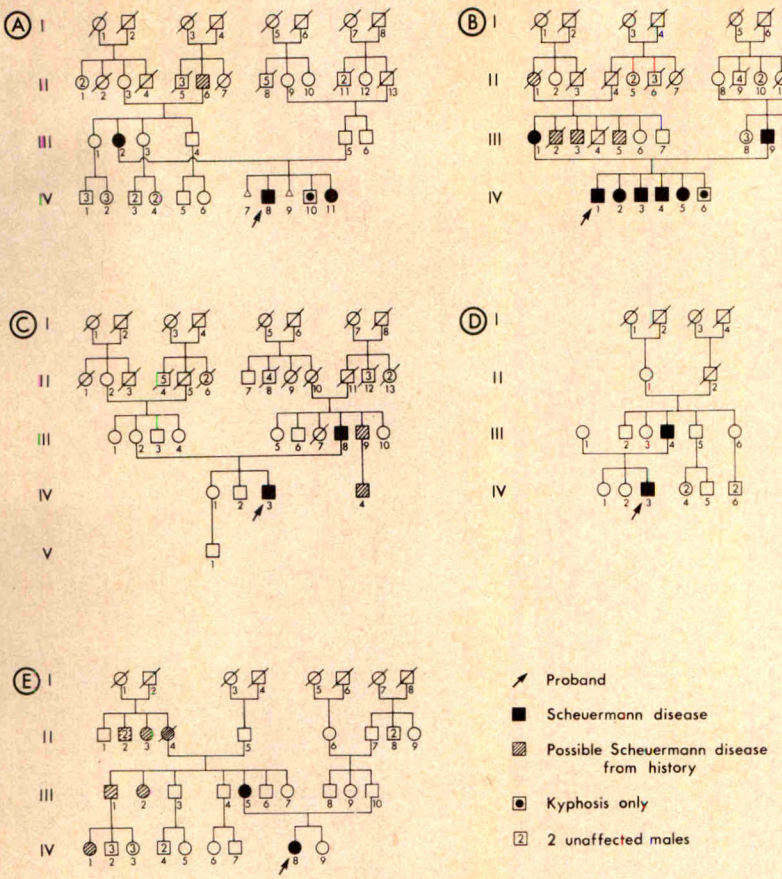
Family D.—Scheuermann's disease was discovered in subject IV-3 after a sports injury to the shoulder at the age of 15. However, his parents had noticed his bad posture since his early teens. After the son was diagnosed, the father (III-4), who also had a mild "round back deformity" but never experienced any back pain, was found to have Scheuermann's disease.

Family E.—The proband (IV-8) was referred to our hospital after she was found to have a "round back" during an annual school check-up. Roentgenographic examination of the spine showed changes compatible with Scheuermann disease. The mother (III-5), who also had a "round back" but no symptoms, had spinal changes diagnostic of Scheuermann's disease. The maternal grandmother (II-4) and three of her siblings (II-2,3) were known as the "round back family" in their hometown.

COMMENT

Several authors have stressed the importance of genetic factors in Scheuermann's disease.[2,4-7] Bradford et al[3] reported that 25% of cases had a positive family history, but the only report in the literature on the mode of inheritance is that of Kewalramani et al.[8] They described Scheuermann's kyphoscoliosis associated with Charcot-Marie-Tooth syndrome in three male members of a family, in three generations. It is not clear, however, whether Scheuermann's disease was inherited as a separate trait in this family or as another expression of the genetic defect responsible for the Charcot-Marie-Tooth syndrome.

The present family studies are compatible with a dominant pattern of inheritance for Scheuermann's juvenile kyphosis. Each proband has an affected parent, and the segregation ratio in the offspring of obligate carriers with unaffected spouses is 17 affected to 27 unaffected, which does not differ significantly from the Mendelian expectation of 22:22 ($P > .05$). The fact that there is a (nonsignificant) deficiency of affected may represent random fluctuation or underreporting. It should be kept in mind, however, that this is a selected series of families. What



Segregation of Scheuermann's kyphosis in five families.

proportion of all cases of Scheuermann's disease will fit this pattern remains to be seen. The expressivity (severity) as seen radiologically varies with age, but in general the clinical expression is fairly mild. Furthermore, there is no evidence of increased severity suggestive of homozygosity in family B. Minimal structural scoliosis is known to occur in about 17% to 36% of patients with Scheuermann's disease.[2,3] A mild scoliosis of about 10° was present in four of our 16 patients.

Since a definite diagnosis of Scheuermann's disease could only be made by means of roentgenographic study, one should be cautious about interpreting a negative family history of an affected person. A round back deformity due to Scheuermann's disease is not always bothersome and does not necessarily lead to a medical consultation. A striking example is given by both parents (III-1 and III-9) of family B. Had the children not been ascertained, the parents would have possibly lived and died without being diagnosed as having Scheuermann's disease.

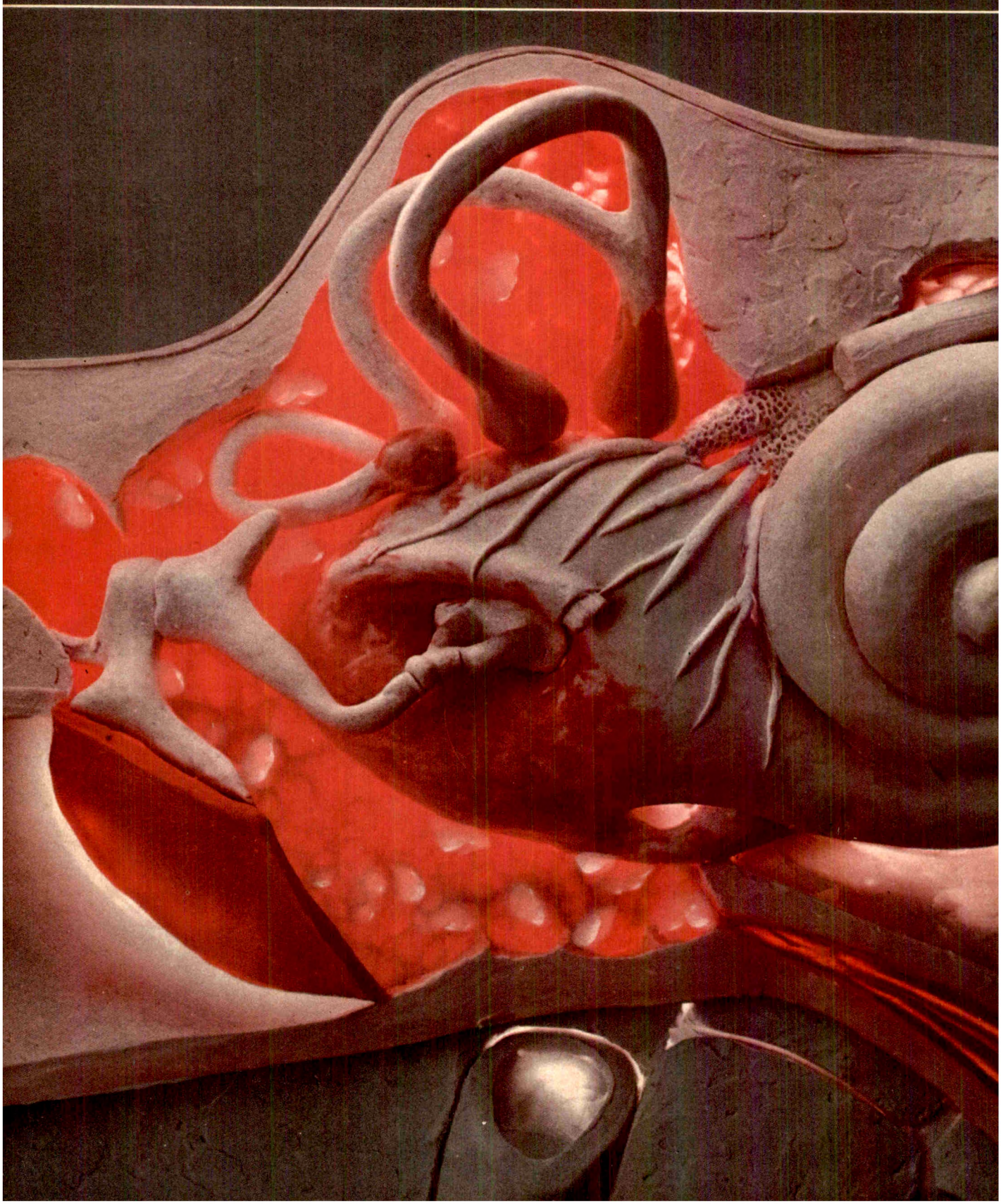
We conclude from this study that Scheuermann's juvenile kyphosis is, at least in some cases, inherited as an autosomal dominant disease with high penetrance and variable expressivity. Further clarification of the genetics of the condition will demand roentgenographic examination of the parents (and other first-degree relatives) of an unselected series of cases. In the meantime, since an appreciable proportion of cases appear to be genetically determined, and since in severe cases, early diagnosis and treatment lead to a more favorable prognosis, offspring of an affected person should be carefully evaluated around the time of puberty.

Sigrid Jequier, MD, assisted with the roentgenographic interpretation. The Medical Research Council of Canada and the McGill University-Montreal Children's Hospital Research Institute provided financial support.

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do those treated with penicillin. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function. Bactrim may prolong prothrombin time in those receiving warfarin; reassess coagulation time when administering Bactrim to these patients.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for infants less than two months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, AND ACUTE OTITIS MEDIA IN CHILDREN:

Adults: Usual adult dosage for urinary tract infections—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days. Use identical daily dosage for 5 days for shigellosis.

Children: Recommended dosage for children with urinary tract infections or acute otitis media—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. Use identical daily dosage for 5 days for shigellosis. A guide follows:

Children two months of age or older:

Weight		Dose—every 12 hours	
lbs	kgs	Teaspoonfuls	Tablets
22	10	1 teasp. (5 ml)	½ tablet
44	20	2 teasp. (10 ml)	1 tablet
66	30	3 teasp. (15 ml)	1½ tablets
88	40	4 teasp. (20 ml)	2 tablets or 1 DS tablet

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	½ the usual regimen
Below 15	Use not recommended

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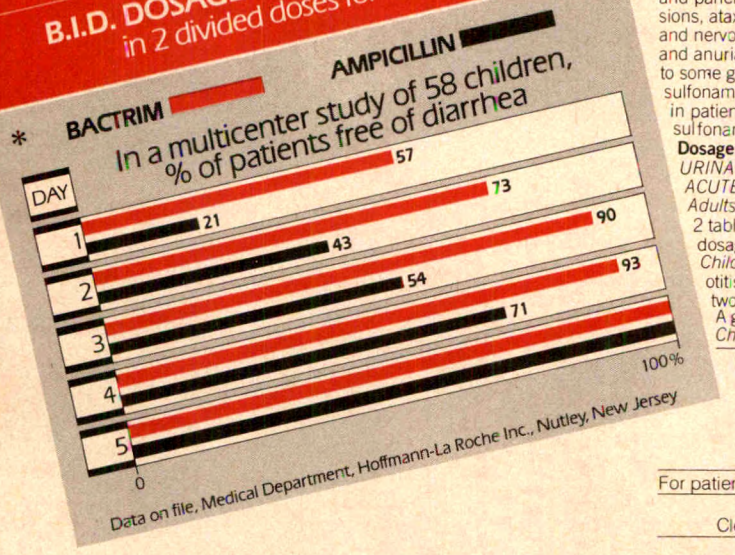
Supplied: *Double Strength (DS) tablets,* each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100; Tel-E-Dose® packages of 100; Prescription Paks of 20. *Tablets,* each containing 80 mg trimethoprim and 400 mg sulfamethoxazole —bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40, available singly and in trays of 10. *Oral suspension,* containing in each teaspoonful (5 ml) the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole, fruit-licorice flavored—bottles of 16 oz (1 pint).

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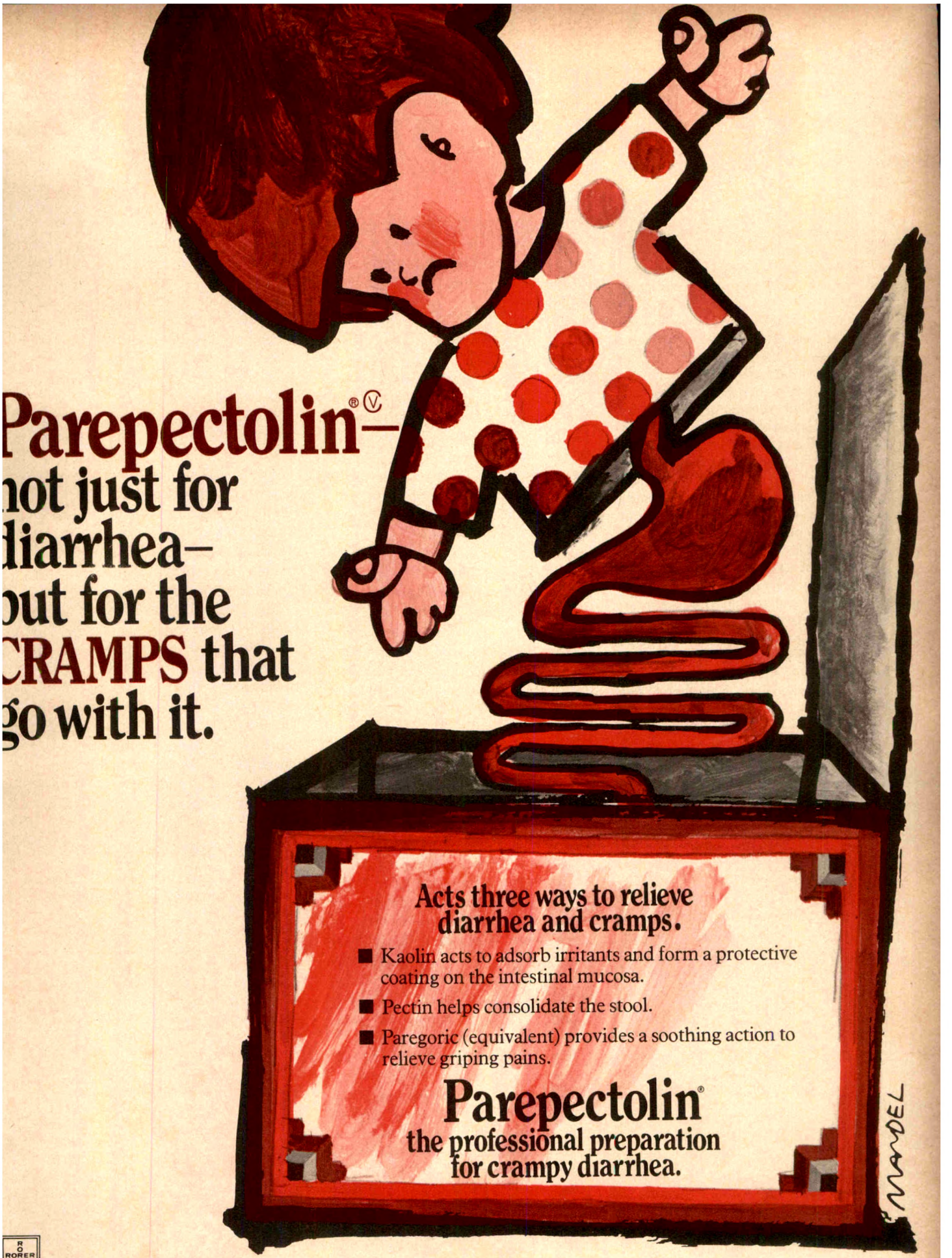
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Studies in Meconium

An Approach to Screening Tests To Detect Cystic Fibrosis

Harry Shwachman, MD; Irena Antonowicz, PhD; Abbas Mahmoodian, PhD; Soto Ishida

• **Screening for cystic fibrosis (CF) in newborns is desirable, and efforts should continue in establishing a system of easily available, reliable, simple, and inexpensive tests. In addition to the Boehringer-Mannheim (BM) test for the detection of albumin, we propose the assay for lactase and β-D-fucosidase in meconium. These latter two enzymes are present in the meconium of babies with CF and absent in meconium of most healthy babies. In a mass screening program for CF involving 20,182 specimens of meconium using only the BM strip, we found 46 positive results. Twenty-nine specimens came from infants with CF, six of whom had meconium ileus. Seventeen specimens yielded false-positive results by the BM test. Eleven of these would have been excluded by the addition of the lactase and β-D-fucosidase assay, thus reducing the false-positive test results by nearly 61%. In a comparative study of the three methods, the lactase and β-D-fucosidase yielded 1.2% false-positives when examined independently. Performance of these two assays may allow greater specificity in diagnosis when used in addition to the BM test.**

(*Am J Dis Child* 132:1112-1114, 1978)

Screening of all newborns for cystic fibrosis (CF) has become widespread in the past three years. Green et al[1,2] demonstrated the presence of serum proteins by chemical and immunologic methods in meconium from babies with CF and its absence in healthy babies and suggested that this finding could be used to detect babies with CF at birth. A simple, rapid, and inexpensive test was developed by Stephan et al[3] for the detection of albumin in meconium. It is known as the Boehringer-Mannheim (BM) test. This is a paper strip test that will detect albumin in meconium greater than 20 mg/g dry weight of meconium. In the majority of babies with CF, the test result is positive (the development of a blue color). A negative reaction in the meconium of healthy infants demonstrates no color development. This test has been performed in the newborn nursery as well as in central laboratories where more accurate testing can be done and where backup procedures are available. The BM test is currently in vogue in many European countries.[4] Its acceptance in the United States is less well received because of (1) a failure to detect all newborns with CF (sensitivity less than ideal), and (2) an unacceptable number of false-positive test results (specificity less than desirable). Every baby whose meconium shows a positive BM test reaction must subsequently have an examination by a pediatrician and a sweat test to establish or exclude the diagnosis of CF.

A recent collaborative study involving seven CF centers sponsored by the Cystic Fibrosis Foundation concluded that mass screening by the BM meconium strip test should not be recommended.[5] A total of 102,159 newborns were screened in the study. Twenty-three cases of CF were found by the BM test and confirmed by sweat tests in addition to six cases of babies with meconium ileus. Four babies with CF were not detected by this test. The incidence of CF in the population studied was 1/4,441. The true incidence in the population examined is unknown but is estimated to be close to 1/2,000. Nearly 1% of the test results were found to be false-positive when the tests were performed in the nursery. This figure was reduced to approximately 0.2% when these same positive specimens were tested in a central laboratory.

The most reliable diagnostic test for the disease is the sweat test, which will identify approximately 99% of those with this disorder. To perform a sweat test in the newborn as a screening test is costly and impractical and an invasive procedure to the nursery, which is ill-advised. However, the sweat test has been carried out in the newborn and infants considered in a high-risk category.

At present the primary biochemical defect in CF is unknown, so that no specific test for the disease has been identified. That lysosomal enzymes behave in an abnormal fashion in CF fibroblasts has been demonstrated by Antonowicz et al[6] and by Hosli et al.[7] Hence, an assay on meconium to include appropriate lysosomal enzymes seems germane.

The purpose of this report is to summarize our experience using the BM meconium test strip and to explore the usefulness of two additional assays that may make screening for CF more specific and reliable. The additional assays include lactase and β-D-fucosidase determinations in meconium. These two tests are simple and inexpensive and can be performed in addition to the BM test by the same person in a central laboratory.

MATERIALS

A total of 20,182 meconium specimens from 12 outlying obstetric hospitals were received by either mail or messenger service between June 5, 1973, and April 5, 1977. The specimens were collected in sealed vials and kept refrigerated until sent to our laboratory. They were obtained routinely from all newborns. More than 95% of mothers were white. We included specimens from high-risk infants, ie, those from families with a CF sibling, first cousins, and infants born to mothers who had CF. Six babies had meconium ileus, and specimens of their meconium were also analyzed. The diagnosis of CF was confirmed by results of sweat tests or pathologic studies. All high-risk babies had sweat tests regardless of the results of the BM test.

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METHODS

The BM test was performed routinely on the meconium using the BM test strips obtained from Boehringer-Mannheim Co. The tests were performed according to the method described by Stephan et al.[3] All positive specimens were tested for occult blood and, if present, were excluded. The babies whose meconium specimens showed a positive BM test result were examined and followed up by one of us (H.S.), with only a few exceptions. A quantitative pilocarpine iontophoresis sweat test was carried out as soon after birth as possible, usually within three weeks of birth. The majority of sweat tests were performed in our clinic by the same experienced person (A.M.). Every meconium specimen with a positive BM test result was analyzed for the presence of lactase and β-D-fucosidase. We also determined the protein concentration. All the determinations were performed on the homogenates of meconium in water, using a dilution of 1:100 (1 mg of meconium homogenized in 0.100 ml of water). The lactase activity was measured using Dahlqvist's method as modified by Antonowicz et al.[8] The β-D-fucosidase activity was measured on the same homogenates according to the method described previously.[9]

Since the aforementioned assays for lactase and β-D-fucosidase are too time-consuming and impractical for screening, we developed a simplified and rapid procedure. The lactase test[10] is performed as follows: A matchtip-sized sample of meconium is placed in a vial to which is added six drops of water and mixed to form a homogeneous mixture. If the BM test is performed first, one adds 0.5 ml of a 3% lactose solution in maleate buffer pH 5.4 to the vial containing the meconium. After a 15-minute period at 37 °C, a dextrose reagent strip is immersed into the solution for a few seconds, removed, and left for color development (for about ten minutes). Blue denotes the presence of glucose derived from lactose hydrolyzed by the lactase present in the meconium. Since lactase is absent in the meconium of healthy infants,[8] a negative test result would tend to rule out CF. A positive lactase test result by this method would include all meconium specimens with a value of more than 2.0 μmole/min/g of protein. An occasional sample of meconium may contain free glucose, and this may be detected by immersing the dextrose reagent strip in the meconium solution without the addition of lactose.

The β-D-fucosidase determination is a semiquantitative assay and depends on the hydrolysis of the substrate p-nitrophenyl-β-D-fucoside (Sigma) by the β-D-fucosidase present in the meconium. In meconium from healthy babies this enzyme is absent.[9] The liberated p-nitrophenol gives a yellow color in alkaline solution. The color is compared with standard solutions of p-nitrophenol. The meconium specimen is prepared by taking a matchtip-sized sample (about 10 mg) with an applicator and mixing it with 1.0 ml of 0.2 M of sodium acetate buffer pH 5.0. Then 0.5 ml of this homogenate is pipetted into a small test tube. The remaining 0.5 ml serves as a blank. To the test homogenate add 0.5 ml of 5 mM p-nitrophenyl-β-D-fucoside (substrate). Add 0.5 ml of water to the blank. The tubes are well shaken and incubated at 37 °C for 15 minutes. The reaction is stopped by adding 0.2 ml of 2 N ammonium hydroxide to both tubes (unknown and blank). After mixing, the yellow color is compared with the yellow color of the standard tubes. The standard tubes consist of different concentrations of p-nitrophenol. The concentrations of p-nitrophenol standards are 0.025, 0.050, 0.100, and 0.200 mM/ml of 0.25N ammonium hydroxide. Since meconium homogenates may be slightly yellow, the unknown is compared with the blank and the deeper yellow reflects the activity of β-D-fucosidase. A comparator block with four holes will serve to match the colors. The meconium blank is placed behind the standard, and the unknown is placed behind the control tube. A positive reaction would be considered a match of colors at 0.025 or above. An alternate method is to use a yellow color chart in place of the slightly more accurate comparator block.

RESULTS

The BM test results were found to be positive in 46 out of 20,182 specimens examined (Tables 1 and 2). Twenty-three of the 46 specimens came from babies who had CF, as confirmed by positive results of quantitative pilocarpine iontophoresis sweat tests.

Six patients had meconium ileus: positive BM test results and the diagnosis of CF were made by sweat tests in four cases and by postoperative pathologic examination in two patients. Seventeen of the 46 specimens were false-positive by the BM test. Eleven of these 17 were negative by

Table 1.—Results of BM and Sweat Tests*

	Positive BM Tests (n = 46)†	Sweat Tests		
		Positive	Negative	Comment
Cystic fibrosis (CF)	23	23	...	CF excluding MI
CF, meconium ileus (MI)	6	4	...	MI, 2 diagnosed postmortem
False-positive	17	...	13	Not CF, 4 not sweat tested

*Abbreviation BM indicates Boehringer-Mannheim.
†Of 20,182 specimens examined, 46 were positive and 20,136 were negative.

Table 2.—Comparison of BM, Sweat, Lactase, and β-D-Fucosidase Tests*

	Specimens Examined	BM Tests		Sweat Tests		Lactase Test		β-D-Fucosidase Test		CF Confirmed by Postoperative Pathologic Examination
		Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative	
CF	23	23	...	23	...	23	...	23	...	...
Meconium ileus	6	6	...	4	...	6	...	6	...	2
CF	4†	...	4	4	...	2	...	2	...	...
False-positive	17	17	...	...	13‡	6	11	6	11	...

*Abbreviation BM indicates Boehringer-Mannheim; CF, cystic fibrosis.
†Only two of the four false-negative BM test specimens were examined for lactase and β-D-fucosidase.
‡Four infants out of 17 were not sweat tested but are clinically well.

Table 3.—Meconium Specimens Tested by BM, Lactase, and β-D-Fucosidase Tests (n = 245)*

BM Tests		Lactase Tests		β-D-Fucosidase Tests	
Positive	Negative	Positive	Negative	Positive	Negative
0	245	3	242	3	242

*Abbreviation BM indicates Boehringer-Mannheim. All sweat test results were negative.

the lactase and β-D-fucosidase assay. The sweat test results of 13 of the 17 babies were in the normal range, four babies were not sweat tested, but on physical examination and follow-up study were found to be healthy, with no stigmas of CF.

Four high-risk babies were found to have negative BM test and positive sweat test results. The diagnosis of CF was made in these four infants, two of whom are under treatment in our CF clinic. Two of these four patients had their meconium tested for lactase and β-D-fucosidase, and the results of both were positive. The other two specimens were discarded before our knowledge that they came from babies with CF.

In six of the 17 specimens that were false-positive by the BM test, the lactase and β-D-fucosidase specimens were also false-positive.

We tested 245 specimens by all three methods, including 42 from high-risk infants who had negative sweat test results. Three of these specimens were negative by the BM test and positive for lactase and β-D-fucosidase and came from non-CF babies (Table 3). Hence, the lactase and β-D-fucosidase assays are also likely to yield false-positive test results.

COMMENT

Screening tests for CF in the newborn period implies that such tests and the detection of the disease at birth would enhance the outcome of patients with a positive diagnosis. Although a few critics will disclaim that early diagnosis makes any difference,[11] we have accumulated evidence in our institution that early diagnosis and treatment indeed do make a difference in morbidity and mortality.[12,13] The mortality in untreated patients at 1 year of age can be well over 60%.[14] In a study[13] that included 76 patients whose diagnoses were made shortly after birth, the survival rate at 1 year of age was 98%. The diagnosis was made before the development of symptoms.

The assumption has been made that the albumin test on meconium would probably fail to detect those babies with CF in whom pancreatic function is unimpaired. Unfortunately, there are no studies reported on the pancreatic function in those babies with CF showing a negative BM test result.

Early diagnosis also has noteworthy genetic implications. Our clinic includes many children in whom a late diagnosis was made. On testing the younger siblings, some were also found to have the disease. In most of these families, restriction of family size would have occurred had the parents been aware of their genetic status. The reduction in the number of false-positive test results by the addition of the lactase and β-D-fucosidase determinations is highly desirable and would avoid the highly emotional and psychological disturbance caused by unreliable or false information.

In a screening program using an immunologic albumin test in meconium, Gottschalk et al reported an experience of 40,000 tests combined with the test for lactase (personal communication, June 1977). The incidence of false-positive test results was reduced from 2.5% to 0.4%. They also encountered one patient who had a negative albumin test result with a positive lactase test result in a patient with CF. This study indicates that the probability of CF with a positive BM test result is 50% (23 out of 46). The probability of no disease with a negative BM test result is 99.8%. Our results suggest that (1) a false-negative albumin test result may yield a positive lactase test result, and (2) the number of false-positive albumin test results can be appreciably reduced by adding the lactase test.

We have not attempted a large screening program using all three methods, but in a small pilot study of 245 specimens, all were negative by the BM tests. Three of these specimens were positive for lactase and β-D-fucosidase. This observation suggests that there is a false-positive rate for lactase and β-D-fucosidase of more than 1%. A large field trial under proper conditions will be required to establish the advantage suggested by our proposal.

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Problem Acuteness and Medical Record Utility

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• **We studied the usefulness of having the patient's medical record available to the pediatrician at the time of the patient's visit. For most acute problems, the medical record had no effect on the management of the patient, whereas the record frequently affected the handling of chronic or recurrent problems. These results suggest a means of improving the effectiveness of pediatric emergency room management and also a means for defining empirically criteria for evaluation of care by record audit.**

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The encounter between a physician and patient has been viewed as a decision-making process requiring information and resulting in diagnostic and therapeutic plans.[1-3] Many factors influence the physician's decisions, including characteristics of the patient, the practitioner, the clinic setting, and medical information itself, especially information recorded in the medical record.[1] Frequently, important information recorded in the chart is not recognized by the physician.[1,4-6]

However, previous research has not determined whether acuteness of the problem influences the usefulness of the information recorded in the chart. Though standard pediatric practice dictates that the patient's old record be examined by the pediatrician during the visit, when he deals with acute problems, the pediatrician frequently makes decisions without examining the record. Moreover, in the emergency room, the old record is rarely examined. However, we suspected that old records do not have a great affect on the management of acute illnesses. We therefore attempted to determine whether acuteness of the patient's illness affected the usefulness of the information in the patient's record for making diagnostic and therapeutic decisions.

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METHODS

Setting

The study was conducted in May and June 1976 in a pediatric clinic that serves as the only pediatric care facility for 1,400 children of 500 families in a southern development town of Israel (population, 11,700). More than 80% of the families cared for are of lower-class, Moroccan, Tunisian, or Indian origin, and parents generally do not have more than a high school education. Although most of the parents can read, many mothers cannot. Moreover, many parents converse mainly in Arabic and speak Hebrew inadequately. Although this population is slowly adapting to the Israeli environment, many of their customs are still determined by their lower-class origin, and include many superstitious explanations of health and disease. (We are from middle class American and South African backgrounds.) When we care for the children of these families, in face of language and cultural barriers, we are beset by many of the frustrations that we have faced when caring for inner city children in the United States.

Children attending the clinic are seen during six morning and four evening clinic sessions spread over six weekdays. All of the evening sessions are for the treatment of severe illnesses, four of the morning sessions are split between visits for acute illnesses and appointments, and the remaining two morning sessions are for "well baby" appointments. At visits for acute illness, the chart can be retrieved with difficulty. However, a patient can always obtain a morning appointment with the chart immediately available within five days of short-term visit.

Of all the problems identified in the clinic over a period of six months, 65.8% could be accounted for by the following six problems: otitis (all forms), 20.3%; impetigo, 13.5%; upper respiratory tract infection, 12%; pharyngitis, 9%; gastroenteritis, 6%; and conjunctivitis, 5%.

Charts

The records of all patients seen by us during six randomly selected morning or afternoon short-term visit sessions were studied. All patients were familiar to both of us. Appointment sessions, including well baby sessions, were not studied. We alternated sessions.

The pediatrician first took a history, examined the child, and recorded the following information on a separate sheet of paper: date, patient's problems, and diagnostic and therapeutic plan before consulting record. To counteract observer bias, an effort was made before consulting the record to identify all problems and to write a complete plan for each problem. Then the record was consulted and the patient's problems and the diagnostic and therapeutic plans were again recorded. After all patients included in the study had been seen, the two sets of plans were compared to determine whether changes in plan had occurred. Changes in plan were defined as changes in problem definition, diagnostic tests ordered, or therapy prescribed. Using this definition of change, the principle investigator (C. Z. M.) and a secretary determined when changes in plan had occurred; they agreed in 100% of the cases. Problems were defined as chronic if they had persisted for more than three months and as recurrent if they had recurred once. If a problem was neither chronic nor recurrent, it was considered acute. All tests of significance were χ^2 tests of homogeneity.

RESULTS

A total of 119 problems were identified in 102 patients. One pediatrician examined 57 patients; the other exam-

Effect of Severity of Illness on Management			
	No. (%)		
	Plan		
	No Change	Change	Total
Acute problems	87 (69.4)	1 (17.5)*	88 (100)
Patients with acute problems	72 (67.5)	1 (14.9)	73 (100)
Chronic or recurrent problems	8 (24.7)	23 (6.3)	31 (100)
Patients with chronic problems	9 (23.5)	20 (6.1)	29 (100)
Total problems†	**95**	**24**	**119 (100)**
Total patients‡	**81**	**21**	**102 (100)**

*Expected observation.
†$\chi^2 = 76.5$; $P < .0005$.
‡$\chi^2 = 57.2$; $P < .001$.

ined 45 patients. The results are summarized in the Table. The difference between changes produced by the record in the diagnostic and therapeutic plans for managing acute problems, as compared with chronic and recurrent problems, is highly significant. The only change in plan in an acute problem was a decision not to order a CBC count in a 2-year-old child with axillary lymphadenitis, since a CBC count had recently been ordered and was within normal limits.

Of the 24 changes in the management plans of chronic or recurrent cases, nine were changes only in diagnostic plan, nine were changes only in the therapeutic plan, and 6 were changes in both diagnostic and therapeutic plans. Of 15 changes in diagnostic plan, 11 were redefinitions of the problem at a higher level of sophistication.

Eleven of 12 diagnostic or therapeutic plans in recurrent problems and 12 of 19 plans in chronic problems were changed after the pediatrician consulted the record. The differences were not significant.

The difference between the number of plan changes made by the two physicians was not significant.

COMMENT

It is standard pediatric practice at least to go through the motions of examining the patient's old record sometime during his visit. However, data collected in this study suggest that in this pediatric clinic, the medical record had almost no effect on the management of the acute problem seen in the practice. On the other hand, the record frequently affected the management of chronic problems, and almost always (11 of 12 times) affected the management of recurrent problems. Although we identified and tried to counteract one bias, namely, that records are not necessarily needed in visits for acute illnesses, unconscious biases may have affected data collection.

These findings can be explained by hypothesizing that when managing acute problems, the pediatrician apparently has no need of extra memory capacity. However, when managing chronic problems, the physician has difficulty remembering old facts that are essential to appropriate decision-making. Moreover, when managing recurrent problems, the pediatrician may find it especially difficult to remember old information, since he has thought of the patient as healthy in the interval between visits. Old information on a chronic problem assumes even greater importance when the pediatrician is seeing a partner's patient.

In view of these findings, a more rational practice would be for paramedical personnel to first determine whether or not a problem is acute, and then to obtain the record only for chronic or recurrent problems. The physician's record of acute problems could be transferred by paramedical personnel to the appropriate record at a later time. In the pediatric emergency room, paramedical personnel might determine whether or not the child has either chronic or recurrent problems. If he has either, the record might be provided routinely to the pediatrician or physician's assistant who sees the patient.

Another use of the research technique of recording plans with and without the record might be to define empirically criteria for evaluation of care by medical record audit. Information in the record that, when provided, causes a change in diagnostic or therapeutic plan should constitute a criterion for evaluation of care by record audit. For example, we noticed that the change in plans for management of two cases of enuresis consisted of, in the first case, an order for a urine culture because of an incomplete examination, and in the second case, for a change in medication because of information in the record about previous medication. Clearly, information on past diagnostic examinations and therapy is critical to the management of enuresis, and the presence of such information ought to constitute a criterion for evaluation by record audit of the care of enuresis. Criteria for evaluation of care determined empirically might be more valid and easier to determine than criteria determined using the self-audit and expert validation technique of Osborne and Thompson.[7] Research should be undertaken to determine the validity and efficiency of recording the plan with and without the record as a technique to specify empirically criteria for evaluation of care by record audit.

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Urolithiasis in Adolescents

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• **The characteristics of 31 adolescent patients aged 11 to 20 years with urolithiasis were examined by means of a ten-year retrospective chart review. The majority of stones were found to be secondary to preexisting conditions, with the most common being bladder dysfunction (neurogenic or exstrophy). Exogenous corticosteroid therapy appeared to play a role in lithogenesis in five patients and was the only apparent contributing factor in an 11½-year-old girl. Childhood inborn errors of metabolism accounted for the stones in four of the teenagers. An additional four adolescents did not have any definable biochemical, genetic, or anatomic abnormalities and, therefore, no obvious etiology.**

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In the spectrum of disorders that affect the urinary tract of adolescents and young adults, stones are uncommon but not altogether rare. Recently challenged by this clinical problem, we found little in the literature that addressed this problem in adolescents, as separate from children and older adults. As it has only been within the last decade that the American Academy of Pediatrics has defined the upper age limits for pediatrics, and a separate interest in adolescents has developed, this circumstance is not surprising. In addition, a variety of medical and surgical subspecialties are involved in the care of these patients.

To develop a rational and effective approach to this uncommon problem in young people, it is then necessary to integrate experience from many sources. For purposes of this review, adolescence is defined chronologically as 12 to 21 years of age and considered to be concomitant with but not limited to the duration of puberty. A review of the available literature at that time did not provide separate data for adolescents and young adults, as the upper age limit in the pediatric studies was 13 to 15 years.[1-7] Information as to the incidence of this problem in the age group from 15 to 21 years had to be sifted from admission records of general hospitals and from military data.[8,9] It was this limitation of information that prompted this retrospective study of all patients aged 11 to 20 years with urolithiasis who were admitted to Childrens Hospital of Los Angeles during a ten-year period from 1966 to 1975.

METHOD

Using the hospital-based computerized chart-retrieval system, all patients with urolithiasis who had been hospitalized between Jan 1, 1966, and Dec 31, 1975, were identified. There were 31 patients in all, 16 males and 15 females, aged 11 to 20 years, with a mean age of 15.1 years. Twenty-nine were white and two black; six of the white patients had Hispanic surnames.

RESULTS

The symptoms of pain in the abdomen or back, hematuria, recurrent urinary tract infections, or routine follow-up of a previous (surgical) urologic procedure prompted the evaluation for stones. The stones were located in the kidney in 12 patients, the bladder in 13, the ureter in five, and both the kidney and bladder in one.

Ten adolescents with neurogenic bladder secondary to myelomeningocele, spina bifida, transverse myelitis, or exstrophy of the bladder comprised the largest group of stone formers in our series. The five patients with exstrophy of the bladder had had multiple reconstructive genitourinary procedures and indwelling drainage devices. Four patients, all males, had stones of undetermined etiology (idiopathic). Two patients had bilateral hydronephrosis secondary to urethral stenosis and recurrent urinary tract infections, three had cystinuria, one oxalosis, and one ileitis; one had stones as a sequela of trauma. Six patients with stones were receiving prolonged steroid therapy: one for

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Table 1.—Composition of Stones

Disease or Condition	No. of Patients	Stone Analysis
Exstrophy of bladder	3	Uric acid, urates, calcium carbonate, calcium oxalate, magnesium phosphate
Neurogenic bladder	3	Calcium phosphate, calcium carbonate, calcium hydrogen phosphate, magnesium ammonium phosphate
Cystinuria	2	Cystine, calcium oxalate, calcium phosphate
Thalassemia major	1	Cystine
Idiopathic	2	Magnesium ammonium phosphate, uric acid, urates, calcium oxalate
Kidney transplants	3	Calcium oxalate, calcium phosphate, calcium carbonate, magnesium phosphate
Oxalosis	1	Calcium oxalate, calcium phosphate
Ileitis	1	Uric acid (100%)
Corticosteroid therapy	1	Calcium oxalate, calcium phosphate

asthma, one for nephrotic syndrome, one for ileitis, and three who had renal transplants.

Seven adolescents had recurrences: three of the neurogenic bladder group, two with cystinuria, one with oxalosis (eight recurrences), and one with exstrophy of the bladder. Two children in one family had idiopathic stones, as did the father.

Staghorn calculi were found in two patients, one with oxalosis and the other with chronic infection. At the time of admission to the hospital, eight of the ten patients with neurogenic bladder had positive urine cultures, as did the three with exstrophy, two with hydronephrosis, and two with renal transplants. All of the adolescents with exstrophy or neurogenic bladder had had a positive urine culture previously. The organisms found were preponderantly *Escherichia coli* and *Pseudomonas*. Other organisms noted were α-streptococcus, enterococcus, *Lactobacillus*, and *Candida*. None of the patients with idiopathic stones had evidence of infection.

Twenty-two of the teenagers had their stones removed by cystoscopic manipulation, pyelolithotomy, or ureterolithotomy. One stone was passed spontaneously shortly after admission to the hospital. Fourteen stones contained calcium, three uric acid, and three cystine; one was pure magnesium ammonium phosphate. The discrepancy in numbers is due to the combination of calcium and uric acid in two cases, and cystine and calcium in one other. In the group with calcium as a component of their stones, none had recorded evidence of hypercalcemia (Table 1).

COMMENT

The first large study of the incidence of calculi in children was made in 1922 by Thomas and Tanner,[10] who polled the members of the American Pediatric and the American Urologic Societies and received reports of stones in 203 infants and children. They concluded that urolithiasis was frequent in infancy and childhood. In 1951, Lattimer and Hubbard[11] reviewed 21,835 admissions to Babies Hospital in New York for a seven-year period and found no cases. The largest series of upper urinary tract stones is from the Mayo Clinic and identifies 78 children over a 20-year period, of whom half were 11 to 15 years old.[7,9] The series of 76 pediatric patients from Boston of Bennett and Colodny[6] included 16 older children with a median age of 13 years. No attempt was made to review experience with stones in pediatric and adolescent populations outside the continental United States and Canada, as all the pathophysiologic contributants to lithogenesis have yet to be identified. Dietary habits, mineral content of water, and racial hereditary factors may play an important pathogenetic role and make a prevalence comparison meaningless.

In our study, there were 16 males (52%) and 15 females (48%). Among the patients of Malek and Kelalis[7] were 49 males (63%) and 29 females (37%) (median age, 9.8 years). Bennett and Colodny[6] found 45 (59%) of 76 patients (median age, 9 years) to be males. Although our figures are at variance with those of these investigators, it is apparent that those studies that include adolescents favor an increased prevalence in males.

As in our study, all reports indicate that whites are more frequently affected than blacks.[12] Our series of 29 white patients and two black patients is consistent with this and disproportionate to the ethnic mix of our hospital population. Thomas,[13] however, suggests that this observation may be true only for idiopathic stone formers, as black patients with hyperparathyroidism or chronic urinary tract infections form calculi with the same frequency as do whites. Also, in contrast to the failure of Daeschner et al[2] to find any Latin-Americans in their stone-forming population, six patients were of Hispanic extraction in our study.

In our group, the largest single association with urolithiasis in adolescents is that of bladder dysfunction, either of neurogenic origin or congenital in nature. Williams and Eckstein[14] state that stones are remarkably common following reconstruction of an exstrophic bladder and may occur either months or years after the surgery. In those individuals with neurogenic bladder, the etiologic factors responsible for the production of stones are chronic infection and hypercalciuria resulting from demineralization of bone secondary to recumbency or protracted immobilization. The latter contributant to stone formation has been amply demonstrated in the past during poliomyelitis epidemics, where calculi developed in a large portion of individuals receiving respiratory assistance.[15] Smith[16] empirically states that adolescents who are immobilized for any reason are at increased risk for this complication and should be monitored carefully.

From our survey and a review of the relevant literature, hyperparathyroidism is rare in adolescents.[17-19] Hypercalciuric states associated with stone disease, then, are unlikely to be due to this cause. Williams[20] notes that in the United States, two thirds of all stones

in the general population are composed of either calcium oxalate or calcium oxalate mixed with calcium phosphate. Stones composed of magnesium ammonium phosphate (struvite) account for only 15% of all renal calculi in adults and occur almost exclusively in patients with recurring urinary tract infections and alkaline urine. Only one of the adolescents in our study had a pure magnesium ammonium phosphate stone, but without evidence of infection or other predisposing factors. Three patients in our series were noted to have either pure uric acid calculi or a uric acid component to their stones. There was no apparent correlation between the primary pathologic condition and uric acid stones.

Smith[16] has summarized the etiologies of nephrolithiasis (Table 2). Although this tabulation includes most of the well-known causes of urolithiasis, numerous other associated conditions were found in the literature. These included the prolonged use of corticosteroids,[21] pyridoxine deficiency, mercury and beryllium poisoning, renal tubular acidosis associated with sulfonamide ingestion,[14] alkaptonuria,[22] Munchausen syndrome,[23] capricious falsification,[24] rhubarb gluttony,[25] ethylene glycol ingestion,[26] overindulgence in Worchestershire sauce,[26] glycinuria,[27] foreign body in the urinary tract,[14] bypass surgery for morbid obesity,[28,29] juvenile rheumatoid arthritis,[30] Henneman-Wallach syndrome,[31] Rubinstein-Taybi syndrome,[32,33] and polycystic kidneys.[34]

In reviewing our data, we were impressed not only by the variety of conditions associated with urolithiasis, but also by the possible contribution of exogenous corticosteroids. It is suggested from our observations and those of others studying the problem of urolithiasis and ileitis that steroid therapy contributes to lithogenesis. Pharmacological doses of steroids are known to accelerate calcium mobilization from bone with resulting hypercalciuria. There also appears to be an impaired absorption of calcium from the gut. While there is no direct effect of steroids on the parathyroids, Williams et al[35] have shown in rats that a secondary stimulation does occur.

Table 2.—Etiologic Classification of Nephrolithiasis*

Renal tubular syndromes
Cystinuria
Renal tubular acidosis (RTA)
Distal tubular defect (type I RTA)
Carbonic anhydrase inhibitors
Enzyme disorders
Xanthinuria
Primary hyperoxaluria
Type I (glycolic-aciduria)
Type II (L-glyceric-aciduria)
Hypercalcemic states
Primary hyperparathyroidism
Sarcoidosis
Immobilization
Hypervitaminosis D
Milk-alkali syndrome
Neoplastic disorders
Cushing's syndrome
Hyperthyroidism
Uric acid lithiasis
Idiopathic uric acid lithiasis
Gout
Myeloproliferative disorders
Low urinary output states
Idiopathic renal lithiasis
Hyperparathyroidism
Urolithiasis associated with gastrointestinal disease
Uric acid lithiasis
Acquired hyperoxaluria
Idiopathic renal lithiasis
Secondary urolithiasis
Infected renal lithiasis
Obstructive urolithiasis

*From Smith.[16]

David et al[36] followed up 64 adult patients for more than one year after renal transplantation. In their patients, hypercalcemia was recorded in approximately one third. The onset of hypercalcemia occurred between one day and one year after transplantation. The severity of the hypercalcemia tended to be worse during the first two weeks after surgery. Once hypercalcemia became manifest, in some cases it persisted as long as two to three years after transplantation. Evidence of persistent hyperparathyroidism with elevated serum parathyroid hormone levels was noted in all of their hypercalcemic patients up to three years after transplantation.

A case of ureterolithiasis diagnosed 11 weeks after transplantation has been recently reported.[37] A review of the literature by the authors indicates that only nine cases of ureteral stone formation in renal transplant recipients had been reported previously, the majority being associated with hyperparathyroidism.

In our series, calculi developed in three girls after renal transplantation. The first patient was an 11-year-old in whom multiple stones developed in the transplanted kidney two years after transplantation. On removal of a nephrostomy tube, debris was noted, and this was believed to be the nidus for the stone formation. The second occurrence was in a 15-year-old with necrosis of the femoral heads and osteoporosis as a complication of steroid therapy. A bladder calculus developed seven months after a second renal transplant. The third was in a 20-year-old, three months' pregnant and receiving steroid maintenance therapy, who had a calculus in the ureteropelvic junction two years after a second transplant.

A previously unreported pathogenic sequence is illustrated by a 19-year-old male in this series with a history of nephrotic syndrome beginning at age 16 years. At that time he had had a percutaneous renal biopsy, and a hematoma, which subsequently calcified, developed in the renal parenchyma. His calculus was discovered after an altercation with the police during which he was hit by a nightstick across the loin producing hematuria. Roentgenograms showed an opaque calculus in the lower pole of the left kidney at the site of the previous biopsy.

Nephrolithiasis is a relatively common complication of chronic granulomatous bowel disease, especially in those patients having the combination of bowel resection and long-term steroid therapy. Our patient was a 15½-year-old boy with ileitis who was receiving steroid therapy for three years and who had a bowel resection at age 13 years. Painless hematuria subsequently developed. Roentgenograms revealed two stones in the ureters of a double collecting system. The stones were removed surgically and were found to be composed of uric acid.

Gelzayd et al[38] reported a series of 885 adult patients with inflammatory bowel disease, 64 of whom had nephrolithiasis. Twelve of these had uric acid calculi. Bennett and Hughes[39] state that stones develop in approximately 4% of patients with ulcerative colitis, and this incidence doubles after colectomy and ileostomy.

The one patient who perhaps most convincingly suggests a correlation between corticosteroid therapy and lithogenesis is an 11½-year-old girl who was treated for severe asthma by her private physician. She had received monthly injections of long-acting steroids for two years before admission for surgical removal of a renal stone. This stone was composed of calcium oxalate and phosphate. No associated renal pathologic condition was demonstrated during her examination.

The persistence of pediatric disease into adolescence is apparent from the four patients with metabolic stones. In the three adolescents with cystinuria, the family history was normal in two and unknown in the one adopted patient. One of these was a 17-year-old girl with thalassemia major who also had multiple gallstones. Although enlarged kidneys have been recorded in thalassemia major and believed to be due to tubular dilation, cystine stones have not. Their presence is genuine evidence of cystinuria.

Although primary oxaluria is a relatively rare genetic disease of glyoxylic acid metabolism, one such patient was identified in our series. This 13-year-old patient had eight admissions since the age of 3 years for recurrent stones. Family history disclosed that both paternal grandparents had kidney problems. In the genetic form of the disease, stones occur rarely, recurrences are frequent, and death may occur from renal failure by age 20 years.

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Maryn Burton assisted in obtaining patient data.

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Basilar Skull Fractures in Children

The Incidence of CNS Infection and the Use of Antibiotics

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• **Forty-six cases of basilar skull fractures in children were reviewed to determine the incidence of CNS infection following injury and the possible value of antimicrobial chemoprophylaxis. The clinical course of the children who were treated with antibiotics was compared with that of patients who received no antimicrobial therapy. Included in the study were patients with hemotympanum alone or with hemotympanum plus additional clinical or roentgenographic signs of basilar skull fracture; patients with tympanic membrane perforation without otorrhea but with blood in the auditory canal; and children with either otorrhea or rhinorrhea. Acute, delayed, or recurrent infection of the CNS did not develop in any of the patients. This study is the first of its kind presented in children. It would seem on the basis of the present series that the systematic use of antibiotic prophylaxis in children with hemotympanum following basilar skull fractures is unwarranted and that children with other signs of basilar skull fractures may have an equally small risk of meningitis following injury.**

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Fractures of the base of the skull represent special problems in children with head trauma. In addition to intracranial hemorrhage, brain edema, and cranial nerve damage, CSF fistulae and other evidence of dural tears are considered major risks. Traumatic dural defects may be manifested by otorrhea and rhinorrhea, as well as hemotympanum and lacerated tympanic membrane with bleeding into the auditory canal but without CSF leaks. These injuries are thought to allow a severe microbial invasion of the CNS.[1-8] This study examines the risk of posttraumatic meningitis in children with basilar skull fractures.

The reported incidence of intracranial infection following basilar skull fractures in adults varies widely.[9-11] Neurosurgical repairs of the dural tears[12] and regimens of antimicrobial chemoprophylaxis have been advocated[6,7,13,14] to avert meningitis. Although neurosurgical repair is now controversial,[12,14] the role of systematic prophylaxis with antibiotics is unclear.

Although, in children, cranial fractures are common with severe head trauma, fractures to the base of the skull are reported to be less common than in adults.[15] The reported incidence of basilar skull fractures in children with head injuries varies from 6% to 14%.[16,17] Hendrick and associates[17] surveyed 4,465 consecutive cases of head trauma in children; they found 241 cases of middle ear injury and only 22 cases of otorrhea and 17 cases of rhinorrhea. Large series, particularly of patients with CSF fistulae, are difficult to collect.

Antimicrobial therapy in children with basilar skull fractures has not been assessed. The present series represents a review of the management of children with basilar skull fractures at the Bronx (NY) Municipal Hospital Center of the Albert Einstein College of Medicine. Its purpose was to determine the incidence of CNS infection following injury and to assess whether the use of antibiotics substantially alters the clinical course.

METHODS

The medical records were reviewed of all patients up to 15 years old who sustained a basilar skull fracture and were admitted to the Bronx Municipal Hospital Center of the Albert Einstein College of Medicine from May 1968 to December 1976. The basis for the diagnosis in head trauma victims was considered appropriate for this study when one or a combination of the following

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criteria were recorded: hemotympanum; tympanic membrane perforation with blood in the auditory canal; otorrhea; rhinorrhea; Battle's sign; hearing loss; clinical evidence of labyrinthitis; or radiologic confirmation of fracture to the base of the skull.

The specific information selected for review in this study were the use of antibiotics, spinal fluid findings, the occurrence of CNS infection, course of hospitalization, and length of follow-up.

RESULTS

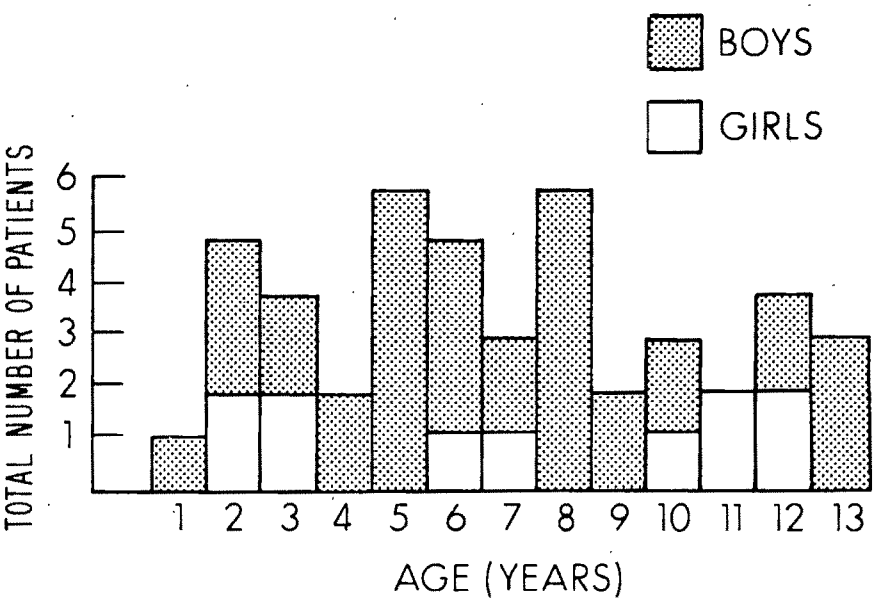
Of 1,315 patients with head trauma admitted to the hospital over the study period, 46 (3.5%) met criteria appropriate for the present study. The ages of the children included in the study ranged from 11 months to 13 years. The distribution varied widely; the ratio of boys to girls was approximately 4:1 (Figure). Motor vehicles were responsible for 40% of injuries; 22% of injuries resulted from falls inside the home (from furniture, stairs, relatives' arms). Falls out of windows and from fire escapes accounted for 17% of injuries. Less than 10% were related to bicycle accidents and other outdoor activities such as tree climbing, playground use, and running.

All children were evaluated in the Pediatric Emergency Room of the Bronx Municipal Hospital Center by pediatric and neurosurgical house officers. Seventy-eight percent were seen within five hours of injury, half of these within the first hour.

Four groups of patients were identified (Table) on the basis of the following presenting signs recorded on admission: group 1, thirty children (65% of the total group) with unilateral hemotympanum alone or hemotympanum plus other findings of basilar skull fractures such as roentgenographic evidence, Battle's sign, or hearing loss; group 2, nine patients (20%) with tympanic membrane perforation with blood in the auditory canal but without CSF leakage from ear or nose; group 3, four patients (9%) with otorrhea; and group 4, three children (6%) with rhinorrhea.

Antibiotic Use

In 14 of the 46 children, antibiotic therapy was started within 24 to 72 hours after admission. The choice of the antimicrobial agent, the dosage, the route of administration, and the duration of therapy, as well as the indication for treatment, varied considerably. The antibiotics used were penicillin or synthetic penicillin derivative (ampicillin or oxacillin or both). Of the 14 children, seven were treated "prophylactically" against possible CNS infection. In three patients, antibiotics were instituted because of temperature elevation despite the finding of normal CSF on lumbar puncture. Three patients were treated with either penicillin G benzathine intramuscularly or penicillin phenoxymethyl orally because of β-hemolytic streptococcal pharyngitis. One patient received a prolonged course of oxacillin intravenously because of a large scalp laceration associated with the skull fracture. Only three of the 14 treated patients received a course of antibiotic therapy that could be considered appropriate in dosage, duration, and route of administration for the treatment of intracranial infection.[18]



Age and sex distribution of 46 patients with basilar skull fractures.

Diagnostic Grouping of 46 Children With Basilar Skull Fractures

Group	Diagnostic Criteria	No. of Patients Treated With Antibiotics	No. of Patients Treated Without Antibiotics	Total
1	Hemotympanum alone or with additional criteria	9	21	30
2	Perforated tympanic membrane with blood in auditory canal but no otorrhea	2	7	9
3	Otorrhea	1	3	4
4	Rhinorrhea	2	1	3
Total		14	32	46

Lumbar Puncture

Lumbar punctures were performed on five of the 14 treated patients and on ten of the 32 untreated children. Indications for lumbar puncture varied. In seven of the 15 who were tapped, the CSF examination was prompted by the development of fever alone. In one additional case, there was fever associated with nuchal rigidity. The remaining lumbar punctures were part of the initial evaluation of the patients or were performed prior to discharge.

All CSF cultures yielded no bacterial growth. Spinal fluid cytologic findings, differential cell counts, and chemistry values were normal in all but one instance. In the latter case, one child in group 2 (tympanic

membrane perforation with blood in the auditory canal but no otorrhea) had a temperature of 37.9 °C and nuchal rigidity on his third hospital day. Cerebrospinal fluid was xanthochromic, containing 120,000 RBCs per cubic millimeter and 550 WBCs cubic millimeter, of which 87% were polymorphonuclear leukocytes. The corresponding peripheral WBC count was 7,600/cu mm, with 70% polymorphonuclear leukocytes. There were no organisms on direct smear or culture. The patient was considered to have a subarachnoid hemorrhage with a reactive pleocytosis. No antibiotic treatment was instituted and the child made an uneventful recovery.

The spinal fluid was not examined in two children who developed temperature elevations. One of these received no antibiotic therapy, while the other was treated for seven days with ampicillin. Both of these children did well.

Outcome

Both the group of 14 children who received antibiotics and the group of 32 who were not treated did equally well. None showed clinical or laboratory evidence of meningitis while in the hospital or during subsequent follow-up.

Seventy-eight percent of the total number of patients were followed up after discharge for periods ranging from a few weeks to several years. The proportion of patients with adequate follow-up was strikingly similar in both the treated and untreated groups. All patients remain symptom free after prolonged follow-up.

COMMENT

The notion that basilar skull fractures are associated with an increased risk of posttraumatic meningitis is based on both anatomical considerations and clinical reports.[1-3] Anatomically, the adhesions between bone and dura are most pronounced at the base of the skull, particularly in childhood.[19] The dura is most apt to rupture with a fracture of the cranial bone to which it adheres. In addition, because of the encasement of the inner and middle ear within the base of the skull and the proximity of the dura to air cells and mucus-lined sinuses,[20] a basilar skull fracture may, in fact, represent an internal or external compound fracture.[17,19,21] As a result, an avenue through the ruptured dura can be created for the invasion of the central nervous system by bacterial flora of the auditory canal, nose, and oropharynx. The clinical findings of rhinorrhea, otorrhea, hemotympanum, and bleeding into the auditory canal through a lacerated tympanic membrane are the major signs of basilar skull fracture and indicate that such an avenue of microbial invasion may have developed.

Rhinorrhea or *otorrhea* provide the most striking evidence of the presence of a dural tear. More subtle, but equally as important are the findings of *hemotympanum* and *bleeding* into the auditory canal with perforation of the tympanic membrane. These indicate the presence of a temporal bone fracture involving the inner or middle ear. The fracture may be longitudinal to the petrous bone or, less commonly, transverse to it. The longitudinal fracture passes through the external auditory canal, middle ear, and mastoid. Perforation of the tympanic membrane with bleeding into the auditory canal is usually present although hemotympanum may be observed.[5-8] The line of a transverse fracture can break through the internal auditory canal, or laterally through the cochlea, and medial wall of the middle ear. Small vessels can bleed into the middle ear space and, with the tympanic membrane intact, hemotympanum occurs. This type of fracture involves the otic capsule, which contains endochondrial bone and heals by fibroplastic proliferation rather than by osteogenesis and thus may leave a pathway for central nervous system infection.[5-8] In either case, fracture and dural rupture around the middle and inner ear may expose the CNS to bacterial flora of the external auditory canal or oropharynx via the Eustachian tubes.

Much of the clinical information suggesting that basilar skull fracture predisposes a patient to posttraumatic meningitis is based on reports of recurrent meningitis secondary to failed healing of dural tissue following injury.[1-3] The reported incidence of acute meningitis following basilar skull fracture, however, varies widely among series. In adults, the occurrence of meningitis following head trauma with rhinorrhea ranges from 0% to 25%.[9-11] When there is otorrhea associated with head trauma the reported incidence is 0% to 9%.[9-11] According to Raaf[9] and Mincy,[22] meningitis is more frequent when rhinorrhea or otorrhea continues for seven days beyond the time of injury. Ignelzi and VanderArk[11] found no instance of posttraumatic meningitis in the 76 adults in their series with hemotympanum or lacerated tympanic membrane with blood in the auditory canal. There are no similar studies of posttraumatic meningitis in children with basilar skull fractures.

With the advent of antibiotics, "routine" chemoprophylaxis became widely accepted in the management of basilar skull fracture.[9,22] More recently, some have abandoned the use of antibiotics for patients with "simple" basilar skull fractures without CSF fistulae, while continuing to use chemoprophylaxis for otorrhea and rhinorrhea.[23] Others recommend antibiotic use following hemotypanum and tympanic membrane perforation with bleeding into the auditory canal.[6,7] Still others believe that antibiotic prophylaxis is of little value in any case.[24]

There have been few studies of the efficacy of chemoprophylaxis in adults with basilar skull fractures. Ignelzi and VanderArk[11] analyzed the results of antibiotic prophylaxis in 129 patients with basilar skull fractures. They found that the therapy did not change the incidence of CNS infection in patients with rhinorrhea, otorrhea, hemotympanum, or lacerated tympanic membrane with blood in the auditory canal, and postulated that chemoprophylaxis may have been harmful in some cases. MacGee and associates[10] reviewed more than 400 cases, combining their own data with findings from the literature, and reported that meningitis occurred in 14% of patients receiving prophylactic antibiotics as compared to 5% of untreated patients. Still another group, Leech and Paterson,[14] studied

155 patients and found that 18% of untreated patients with otorrhea developed meningitis, but only 5% of similar patients who received antibiotics became infected. In this series, none of the patients with rhinorrhea developed meningitis after receiving adequate doses of antibacterial therapy from the onset, while 16.6% of untreated or inadequately treated patients developed infections. Patients with hemotympanum or lacerated tympanic membrane with bleeding in the auditory canal were not studied in the series of Leech and Paterson or MacGee and colleagues.

The present study comprised a group of 46 patients justifiably considered at risk for direct contamination of the subdural spaces by virtue of the signs of rhinorrhea, otorrhea, hemotympanum, or perforated tympanic membrane with blood in the auditory canal. Of the 46 children with basilar skull fractures, none developed CNS infection. Those who received no antibiotics during their entire course of hospitalization represented 57% of the total group (Table). The untreated children did as well as those who were given antibiotic therapy as "prophylaxis" to prevent intracranial infection or for other reasons such as the treatment of an intercurrent streptococcal pharyngitis.

In our series, children with basilar skull fractures experienced no difference in risk of posttraumatic meningitis whether or not they were treated with antibiotics. The relative risks within and between each diagnostic group are more difficult to assess. Group 1, children with posttraumatic hemotympanum, is the largest group. The 21 untreated patients did as well as the nine patients treated with antibiotics. None showed evidence of acute, delayed, or recurrent CNS infections. These results compare favorably with those of Ignelzi and VanderArk.[11] In their series, 34 untreated and 25 treated patients with hemotympanum remained free of infective complications. No other studies of hemotympanum following head trauma are available and none have evaluated the incidence of posttraumatic meningitis in children. It would seem, however, that the uniformly good outcome of the patients with hemotympanum in the present study speaks against the routine chemoprophylaxis in children with this particular injury.

The absence of infection in groups 2, 3, and 4 is encouraging but not conclusive because of the small number of patients. It remains unclear whether these groups are at genuine risk of meningitis, whether these risks are equal in adults and children, whether the duration of CSF leakage enhances that risk, and whether chemoprophylaxis changes that risk.

While our series of patients is comparatively small, it is the first to our knowledge to assess the outcome in children assigned to groups according to the type of manifestation of basilar skull fracture and further subdivided by antibiotic use. Although some of the diagnostic groups are small, the uniformly good long-term outcome of all patients after hospital discharge establishes the need for a larger prospective study of children with basilar skull fracture. This review suggests that routine prophylaxis in children with basilar skull fracture as evidenced by hemotympanum alone is unnecessary and that it may be unwarranted in all cases of basilar skull fractures.

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Avascular Necrosis of Bone After Renal Transplantation

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• **Avascular necrosis (AN) of bone developed in 11 of 100 children who received renal transplants from 1964 to 1977. Bones involved were femoral heads, 14; femoral condyles, 12; tali, two; and carpal naviculars, two. Seven children with symptomatic AN of the femoral heads were treated with limited weight bearing; three subsequently required arthroplasty, and degenerative joint disease developed in one. The AN at other joints healed clinically but not roentgenographically. Although the prevalence of AN decreased after 1967 coincident with a decrease in prednisone dose, children with AN received the same cumulative prednisone dose as children in a control group. Serum phosphorus levels were different in the AN and control groups, but other indexes of hyperparathyroidism were similar. The relative contributions of prednisone therapy and hyperparathyroidism to the development of AN could not be delineated.**

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Over the past 15 years, renal transplantation has become an accepted form of treatment of children and adults with end-stage renal disease. Avascular necrosis (AN) of bone is a fairly common and frequently disabling complication of transplantation in adults,[1-9] but there have been no detailed reports concerning its occurrence in children. Although some of the factors predisposing to its development are recognized, the precise cause is unknown. The natural history and the response to conservative management are likewise obscure. We have examined the incidence of AN in a large group of children after transplantation, have analyzed the factors that may contribute to its development, and have observed its course, with and without treatment, over periods of from one to 12 years.

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PATIENTS AND METHODS

Between April 1964 and January 1977, 100 children, 2 to 16 years of age, received kidney transplants that functioned for at least three months. The diagnosis of AN was made in 11 of these children on the basis of characteristic roentgenographic findings. In ten, the diagnosis was suspected clinically and confirmed by roentgenograms of the hips, knees, or both, whereas in one asymptomatic patient, AN of the femoral heads was visualized on an intravenous (IV) urogram. The IV urograms were performed in most of the 100 children and were reviewed for the presence of AN. The period of follow-up in the 11 children with AN extended through December 1977.

At the time of transplantation, treatment with prednisone, 2 to 4 mg/kg, and azathioprine, 2 to 3 mg/kg, is started for all children in our institution. From 1964 through 1971, short courses of dactinomycin and irradiation to the kidney were given, and in 1970 to 1974 a few children received antilymphocyte globulin. The prednisone dose is rapidly decreased to 0.8 to 1.0 mg/kg at the end of one month and more slowly thereafter to a minimum dose of 0.1 to 0.3 mg/kg. Since June 1970, therapy for children with good renal function has been changed to an alternate-day prednisone regimen at six months after transplant.[10] Rejection episodes are treated by increasing the dose of prednisone; before September 1972, pulse doses of IV methylprednisolone were also given for rejection.[11]

For analysis of factors contributing to the development of AN, each patient with AN was matched with a control patient for the following characteristics: sex, age, date of transplantation, number of transplants, and donor source (living related or cadaver). Whenever possible, the following data were obtained in each patient and compared in the two groups: duration of renal failure and duration of dialysis before transplantation; predialysis serum calcium, phosphorus, alkaline phosphatase, and parathyroid hormone (PTH) levels before transplantation; roentgenograms of bone before transplantation; mean serum calcium, phosphorus, alkaline phosphatase,

and creatinine levels after transplantation until the diagnosis of AN was made or during similar periods in the control patients; serum PTH levels and roentgenograms of bone at the time of diagnosis of AN or at a similar period in the control patients; and the cumulative dose of prednisone received at three, six, 12, and 24 months after transplantation and the total dose received until the diagnosis of AN was made or during similar periods in the control patients. The duration of follow-up was the same in both groups.

Renal osteodystrophy was diagnosed from the characteristic roentgenographic changes of rickets and secondary hyperparathyroidism; secondary hyperparathyroidism was the preponderant finding in all children with osteodystrophy. Serum PTH level was measured by radioimmunoassay in three laboratories with different normal values during the 13-year course of this study; 18 of 24 measurements were made with an assay that recognizes both short- and long-acting sequences of the PTH molecule and detects acute changes in serum PTH levels in uremic patients.[12]

RESULTS

The clinical data of the 11 children with AN are shown in Table 1. All patients were recipients of first transplants, with the exception of patient 7 who received a second transplant. Patient 10 had rejected the transplanted kidney, and dialysis was started again four months before the onset of symptoms of AN. The mean age of the patients, 11.3 years, and the sex ratio, five boys: six girls, were similar to the mean age of the 100 children who received transplants, 10.6 years, and the sex ratio, 51 boys: 49 girls. The ratio of children receiving living related donor kidneys to cadaver kidneys, 8:3, was greater than the ratio in the total population, 46:54, but this difference was not statistically significant.

With the exception of patient 8, all patients with AN of the femoral heads or femoral condyles presented with pain in the involved joints. The AN of the tali and carpal navicular in patient 1 was asymptomatic. In two children, roentgenograms taken at the onset of initial symptoms were normal. In patient 2, roentgenograms were normal at one and five months after the onset of symptoms and demonstrated AN at 11 months. In patient 10 roentgenograms were normal initially and at two months, a bone scan showed AN of both femoral heads at five months, and roentgenograms demonstrated AN on the right at eight months and on the left at 15 months.

TREATMENT AND COURSE

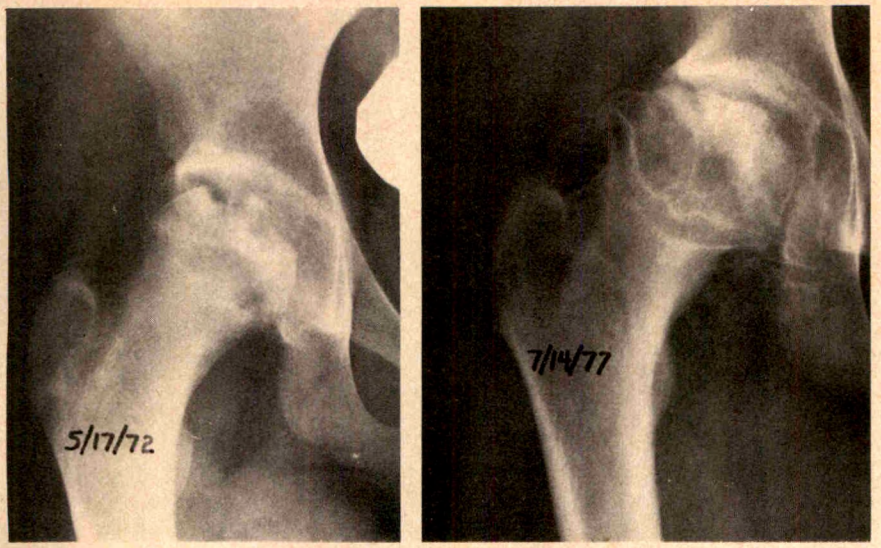
The seven children with symptomatic AN of one or both hips were treated with limited weight bearing when the diagnosis was established. Three of these children subsequently required hemiarthroplasty or total arthroplasty because of progressive collapse of the femoral heads and pain. Patient 1, who had involvement of both hips, had insertion of an Austin-Moore prosthesis on the left after 15 months. Twelve years later she was asymptomatic, and roentgenograms showed healing, with sclerosis of the right femoral head. Patient 2 had a total hip replacement after 72 months and was asymptomatic 3½ years later. Patient 10 was scheduled for a total hip replacement on the right after 11 months in December 1977; she had mild changes of AN on the left that had not progressed. In two patients (5 and 6) pain disappeared, but roentgenographic changes of AN progressed. Patient 5 died after 18 months, and patient 6 had degenerative joint disease five years later (Figure). Two patients (9 and 11) were being treated with limited weight bearing in December 1977, and both showed roentgenographic progression of AN. The only patient with asymptomatic AN of the hips (patient 8) was not treated and demonstrated complete roentgenographic healing within three years.

Symptoms of AN of the knees

Table 1.—Clinical Data

Patient	Age at Transplant, yr	Sex	Donor	Date of Transplant	After Transplantation: Onset of Symptoms, mo	After Transplantation: Diagnosis, mo	Prednisone, mg/day: At Diagnosis	Prednisone, mg/day: At Follow-up	Bones Involved
1	14	F	Mother	5/64	4	9	5	7.5*	Both femoral heads; both tali; both carpal naviculars
2	16	F	Mother	11/66	5	16	20	15*	Right femoral head; left femoral condyle
3	5	F	Grandmother	12/66	46	55	60†	15†	Both femoral condyles
4	7	F	Grandmother	1/67	45	54	60†	15†	Both femoral condyles
5	15	M	Father	5/67	1	5	20	30‡	Both femoral heads
6	13	F	Mother	11/70	14	14	60†	15†	Both femoral heads; both femoral condyles
7	12	M	Cadaver	1/71	36	36	30	0	Both femoral condyles
8	5	M	Mother	8/71	...	5	20	5	Both femoral heads
9	13	M	Mother	6/73	33	33	12.5	0	Both femoral heads; both femoral condyles
10	9	F	Cadaver	7/75	9	17	0	0	Both femoral heads; left femoral condyle
11	15	M	Cadaver	12/75	10	12	15	12.5	Right femoral head

*At operation for hip prosthesis.
†Alternate-day dose.
‡At death.



Left, Initial roentgenogram of patient 6. Mottled lysis and sclerosis of femoral head accompanied by fragmentation and mild collapse. Right, Five years later, there is progressive collapse accompanied by severe secondary degenerative joint disease and remodeling of femoral neck and acetabular roof.

Table 2.—Prednisone in Avascular Necrosis and Control Patients

	Avascular Necrosis Patients	Control Patients
No. of patients	11	11
No. receiving prednisone in year before transplant	2	3
Mean cumulative prednisone dose, mg/sq m		
3 mo	3,368	3,466
6 mo	5,018	4,211
12 mo	8,336	8,086
24 mo	11,893	14,087
Total dose	14,207	12,432

Table 3.—Possible Etiologic Factors in Avascular Necrosis

	Before Transplant		After Transplant	
	Avascular Necrosis Patients	Control Patients	Avascular Necrosis Patients	Control Patients
Serum calcium level, mg/dl*	8.9 ± 1.4	9.3 ± 0.7	10.1 ± 0.9	9.9 ± 0.8
Serum phosphorus level, mg/dl*	7.1 ± 2.8	5.2 ± 1.4†	3.0 ± 0.7	4.2 ± 1.5‡
Serum alkaline phosphatase level, IU/liter*	118 ± 69	120 ± 91	81 ± 40	105 ± 68
Ratio of patients with elevated parathyroid hormone level	4:5	4:6	4:7	2:6
Ratio of patients with osteodystrophy	6:9	3:9	5:9	1:7
Duration of renal failure, mo*	37.6 ± 38.5	16.0 ± 9.7	. . .	. . .
Duration of dialysis, mo*	3.8 ± 3.7	2.8 ± 3.3	. . .	. . .
Serum creatinine level, mg/dl*	. . .	. . .	1.8 ± 1.0	1.3 ± 0.5

*Mean ± SD.
†For difference between groups, $P < .05$.
‡For difference between groups, $P < .02$.

regressed spontaneously and only two patients (3 and 4), who were sisters, were treated with limited weight bearing. Although residual changes of AN have persisted on roentgenograms in all cases, there has not been progression to collapse or degenerative joint disease. The AN of the tali and carpal naviculars in patient 1 has remained asymptomatic for 12 years, although roentgenographic changes persist.

CONTRIBUTING FACTORS

A comparison of the amount of prednisone received by the children with AN and the children in the control group is shown in Table 2. There was no difference between the groups in the number of children receiving prednisone in the year before transplantation and in the mean cumulative dose of prednisone per square meter at three, six, 12, and 24 months after transplantation and in the total dose received. The number of children who received pulse doses of methylprednisolone was similar in the two groups.

Data pertaining to calcium and phosphorus metabolism and renal failure in the two groups are shown in Table 3. In the children with AN, the mean serum phosphorus level was significantly higher ($P < .05$) before transplantation and significantly lower ($P < .02$) after renal transplantation than in the control children. Although a higher percentage of children with AN had roentgenographic evidence of hyperparathyroidism both before and after transplantation, these differences were not significant, and there were no significant differences in serum calcium and alkaline phosphatase levels and the percentage of children with elevated PTH levels, either before or after transplantation, in the two groups. The duration of renal failure was greater in the children with AN, but this difference was not significant. The duration of dialysis and the serum creatinine level after transplantation were similar in the two groups.

COMMENT

Avascular necrosis, primarily affecting the femoral heads and femoral condyles, developed in 11% of children after transplantation. The mean age of the children at diagnosis was 13 years, which is older than the age at which AN of the femoral head develops in normal children, 4 to 10 years, but is similar to the age of children with AN reported from another transplant center.[17] The incidence of 11% compares with incidences of 0% to 20% reported from six pediatric transplant programs,[8,13-17] and 6% to 34% in programs in which most of the patients were adults.[1-8] In ten of the children, the diagnosis was confirmed on roentgenograms taken after the

children complained of pain in the hips or knees. Although roentgenographic bone surveys were not routinely obtained and some asymptomatic cases may have been missed, IV urograms were performed in most of the 100 children, and review of these films disclosed unsuspected AN of the hips in only one child.

Several factors may lead to confusion in the diagnosis of AN. Many patients have complaints of nonspecific musculoskeletal pain in the immediate months after transplantation, which may be mistaken for the pain of AN.[18] On the other hand, the pain of AN may appear a number of months before the diagnosis can be confirmed roentgenographically. Patient 10 in this series had hip pain for eight months before the characteristic roentgenographic changes of AN appeared, although a technetium Tc 99m methylene diphosphate bone scan showed decreased uptake in the femoral heads after five months. Bone scans have been reported to be more sensitive than roentgenograms in detecting AN, and, in a recent study,[19] 12 of 27 patients had abnormal fluorine 18 scans of the hips after transplantation, and roentgenographic evidence of AN eventually developed in four.

The recommended treatment for AN of the hips and knees is limited weight bearing, but there are few data concerning the effects of this treatment and the long-term course of AN in patients after transplantation. The necessity for hemiarthroplasty or total arthroplasty in AN of the hips in adults has varied from 22% to 75% in four series,[1,4,6,9] whereas surgical treatment has seldom been necessary for AN at other joints. Four out of five affected femoral heads and one humeral head were replaced in children at Los Angeles Childrens Hospital.[20] In our series, symptoms of AN of the knees resolved regardless of treatment, and, although roentgenographic findings persisted in every case, there was no progression to degenerative disease during the period of follow-up. On the other hand, the seven children with symptomatic AN of the hips, all of whom were treated with limited weight bearing, showed roentgenographic progression of the lesion. Three required hip replacement, one of them seven years after the onset of symptoms, and a fourth has severe degenerative joint disease six years after the onset of symptoms. During the period of observation of one to 12 years, only three of 14 affected hips showed roentgenographic healing, and AN had been an incidental finding in two of these.

Avascular necrosis was first described in a patient treated with adrenal corticosteroids in 1957,[21] and the association of AN and corticosteroid therapy has subsequently been documented in a variety of clinical settings. Avascular necrosis has also occurred in patients with Cushing's disease,[22] and there is considerable evidence that corticosteroid therapy is the primary factor involved in the development of AN after transplantation. In a previous report from our institution including adults and children, Harrington et al[2] found that the incidence of AN decreased from 32% to 2% after March 1967, coincident with a reduction in steroid dose from 3.0 g to 1.2 g during the first three weeks after transplantation. We have confirmed this relationship in the present series: AN developed in four of seven children who received transplants before March 1967, whereas AN developed in only seven of 93 who received transplants after March 1967. Similarly, in a review of published cases from nine centers, Ibels et al[8] found that there was a correlation between the mean prednisone dose during the first month after transplantation and the incidence of AN.

Despite these findings, many investigators have noted conspicuous variability in the amount of prednisone received by patients in whom AN develops and have been unable to find a difference between the prednisone dose of those in whom AN developed and those in whom it did not. In six studies[3,4,7-9,17] in which the dose of prednisone was compared in patients with AN and controls after transplantation, in only one[3] was a relationship between prednisone dose and AN demonstrated. Comparing patients with AN and controls matched for age, sex, donor source, and date of transplant, we could find no difference in cumulative prednisone dose at 3, 6, 12, and 24 months after transplantation and the total dose received. A case in which a recipient of a transplant from an identical twin did not receive any corticosteroid therapy but in whom AN nevertheless developed has been reported.[23]

Because of the equivocal relationship between prednisone dose and AN, several investigators have suggested that other factors, such as abnormal calcium and phosphorus metabolism and secondary hyperparathyroidism, may also contribute to the development of AN after transplantation. Briggs and associates[3] showed that eight of 11 patients with AN after transplantation had roentgenographic evidence of secondary hyperparathyroidism before transplantation compared with one of ten control patients. After transplantation, the serum calcium levels were higher and the serum phosphorus levels lower in the AN than in the control patients at six to 18 months, suggesting the persistence of secondary hyperparathyroidism in the AN patients. Chatterjee and associates[24] found that the incidence of AN was 44% in patients with biochemical evidence of hyperparathyroidism after transplantation compared with 7% in patients without such evidence, and Ibels et al[8] found histologic changes of hyperparathyroidism as well as osteoporosis in the bones of patients undergoing arthroplasty for AN.

In our series, the increased serum phosphorus level before transplantation and the decreased serum phosphorus level after transplantation in patients with AN suggest a relationship between hyperparathyroidism and the development of AN. The fact that five of nine patients had roentgenographic evidence of hyperparathyroidism at the time AN developed whereas only one of seven control patients had hyperparathyroidism at a comparable period after transplantation is also suggestive, although this difference was not statistically significant.

It is of interest that AN of the hips progressed despite a decrease in prednisone dosage in five of the patients, including two in whom prednisone

therapy was discontinued when dialysis was started again. It is also noteworthy that three patients were receiving alternate-day steroids when AN was diagnosed, and in one of these, AN progressed for five years despite low-dose alternate-day therapy. This is similar to the experience of Reed and associates[25] who found no roentgenographic improvement in AN when prednisone therapy was changed from daily to alternate-day. Although it has recently been reported that abnormal bone scans for AN can revert to normal when prednisone is changed from daily to alternate-day therapy,[19] it appears that AN of the hips that has reached the stage of roentgenographic recognition is frequently irreversible and may progress despite changes in therapy designed to alleviate the underlying cause.

William Murray, MD, cared for many of the patients.

Nonproprietary Names and Trademarks of Drugs

Azathioprine—*Imuran.*
Dactinomycin—*Cosmegen.*

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Strongyloidiasis in Childhood

Joseph A. Burke, MD

• *Strongyloides stercoralis* is an intestinal nematode of man that is still regularly encountered in many parts of the United States. Strongyloidiasis should be considered in any child with unexplained eosinophilia, steatorrhea, protein-losing enteropathy, or chronic diarrhea, especially if associated with weight loss, growth failure, or recurrent upper abdominal pain. This parasite should be ruled out in any patient from an endemic region who is to be treated with corticosteroids or immunosuppressive agents. Microscopical examination of duodenal fluid, Baermann's fecal extraction technique, or the Haradi-Mori stool culture method may be required to make a diagnosis because the organism is not routinely found in concentrated feces even after multiple examinations in some infected individuals. A diagnosis of strongyloidiasis is important because the disease is curable.

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Strongyloidiasis is endemic in many rural areas in the southern part of the United States.[1,2] Occasional cases have been seen in northern parts of the country.[3] It is expected that imported strongyloidiasis will be encountered with increasing frequency in the North and in metropolitan areas because of recent demographic factors, such as extensive migration from the rural South to industrial areas, the large influx of immigrants to urban centers from endemic regions such as Puerto Rico and Mexico,[4] and the recent residence of large numbers of American servicemen in endemic areas of southeast Asia.[5] Once an infection with *Strongyloides stercoralis* has been acquired, the parasite may persist in its host for decades via the cycle of autoinfection.[6]

Although many individuals infected with *S stercoralis* are asymptomatic, this parasite can cause a broad spectrum of clinical manifestations.[7-9] Recent reports suggest that strongyloidiasis produces more disease than currently appreciated.[10-12] Seventeen cases of strongyloidiasis were diagnosed at the University of Kentucky Medical Center, Lexington, during 1976. A lack of awareness of the spectrum of symptoms associated with *S stercoralis* infection and the fact that the disease may be difficult to diagnose account for many overlooked cases.[13,14] In addition, depressed delayed hypersensitivity as a result of intercurrent disease, malnutrition, corticosteroids, or immunosuppressive drugs may convert an unrecognized asymptomatic infection into a potentially lethal massive hyperinfection.[10]

The purpose of this report is to direct attention to the problem of strongyloidiasis. Increased awareness of the possibility of strongyloidiasis in children should lead to earlier diagnosis and improve the prognosis of this potentially lethal,[15] but treatable, parasitic infection. Five children who were evaluated and treated at the University of Kentucky Medical Center are described to illustrate important clinical, diagnostic, or therapeutic points. The discussion reviews the morphology and life cycle of *S stercoralis* and the epidemiology, clinical manifestations, pathology, diagnosis, and treatment of strongyloidiasis.

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REPORT OF CASES

Case 1.—This patient was hospitalized at 8½ years of age because of intermittent

crampy upper abdominal pain of 17 days' duration. There was a two-week history of anorexia, lethargy, vomiting, and diarrhea. The stools looked like pea soup and numbered three to five per day. He had lost 2.7 kg. On admission, the patient weighed 23 kg (15th percentile) and was 124 cm tall (25th percentile). Results of the physical examination were normal, except for a moderately distended abdomen and mild epigastric tenderness.

Laboratory findings included the following values: hemoglobin, 13.4 g/dl; hematocrit, 40%; WBC count, 50,200/cu mm, with 8% neutrophils, 78% eosinophils, 12% lymphocytes, and 4% monocytes. The feces was positive for occult blood. A stool culture was negative for enteric pathogens. Three stool specimens were negative for parasites. Rhabditiform larvae of *S stercoralis* were found in his fourth stool specimen. An enzyme-linked immunosorbent assay for *Toxocara* was negative. Chest and upper gastrointestinal tract roentgenograms were normal.

The patient was treated with thiabendazole, 25 mg/kg of body weight twice daily for two days. The vomiting, diarrhea, and abdominal pain stopped two days after therapy was instituted. When evaluated five weeks later, the patient was asymptomatic and had gained 2.3 kg. His WBC count was 8,400/cu mm, with 4% eosinophils.

Epigastric pain, vomiting, diarrhea, and weight loss are prominent symptoms in many children. This case also demonstrates that an eosinophilic leukemoid reaction may occur in strongyloidiasis.

Case 2.—A female infant weighed 3.5 kg at birth. During the first month of life, she developed nonbilious vomiting. The patient was hospitalized at 6 months of age because of intermittent vomiting and failure to thrive. There was no history of pulmonary disease, diarrhea, or abdominal pain. On admission, the infant weighed 3.9 kg (less than the third percentile) and was 58 cm long (less than the third percentile). She had decreased subcutaneous tissue, generalized muscle wasting, and a distended abdomen.

The results of a complete blood cell count were as follows: hemoglobin level, 15.6 g/dl; hematocrit value, 46%; WBC count, 22,400/cu mm, with 13% neutrophils, 8% band forms, 12% eosinophils, and 67% lymphocytes. A repeated WBC count several days later was 21,600/cu mm, with 28% eosinophils. A stool culture was negative for enteric pathogens. Sedimentation rate and serum immunoelectrophoresis values were normal. Two stool specimens contained rhabditiform larvae of *S stercoralis*. A chest roentgenogram was normal.

During the first ten days in the hospital, she gained only 105 g and had five to 11 loose, green or brown, foul-smelling stools per day. Twelve days after admission, the patient was treated with thiabendazole, 25 mg/kg of body weight twice daily for two days. She gained 1,025 g during the ensuing 12 days and the diarrhea ceased. Figure 1 shows her subsequent weight gain.

Marked growth failure and vomiting were the predominant symptoms in this infant. These problems were promptly reversed by appropriate therapy. How this patient acquired strongyloidiasis so early in life is unknown. It is possible she became infected at birth.

Case 3.—A 7½-year-old boy was referred because of anorexia, diarrhea, and upper abdominal pain of two weeks' duration. He had lost 0.9 kg. There was no history of cough or wheezing. Results of the physical examination were normal.

The WBC count was 17,400/cu mm, with 52% neutrophils, 3% band forms, 21% eosinophils, 20% lymphocytes, and 4% monocytes. Chest roentgenogram was normal. A stool culture was negative for enteric pathogens. Four stool specimens were negative for parasites. A sample of duodenal contents was obtained with a length of nylon yarn coiled inside a weighted gelatin capsule.[14-16] The duodenal sample contained rhabditiform larvae of *S stercoralis*.

The patient was treated with thiabendazole, 25 mg/kg of body weight twice daily for two days. When evaluated one month later, the patient was asymptomatic. The WBC count was 10,600/cu mm, with 4% eosinophils.

In this case, microscopical examination of duodenal fluid was necessary to establish a diagnosis because four stool examinations were negative for *S stercoralis*.

Case 4.—A female child was hospitalized at 4 years and 11 months of age for evaluation of short stature. There was no history of vomiting, diarrhea, or abdominal pain. Physical examination disclosed a lethargic child, with a hoarse cry and a protuberant abdomen. She weighed 16.3 kg (25th percentile) and was 86 cm tall (less than the third percentile).

The serum thyroxine level was 2.7 μg/dl (normal, 5 to 12 μg/dl); the triiodothyronine level was 112 ng/dl (normal, 72 to 215 ng/dl); the thyroid-stimulating hormone concentration was greater than 100 μU/ml (normal, less than 10 μU/ml). An iodine 131 radioisotope scan showed no radioactive iodine in the region of the lower neck. There was a small amount of radioactivity in the midline at the base of the tongue. The child's short stature was attributed to hypothyroidism secondary to an embryological defect resulting in a small sublingual thyroid gland. She was treated with levothyroxine sodium.

The results of a complete blood cell count obtained at the time of admission to the hospital were as follows: hemoglobin level, 11.7 g/dl; hematocrit value, 33%; WBC count, 10,400/cu mm, with 22% neutrophils, 3% band forms, 23% eosinophils, 45% lymphocytes, and 6% monocytes. A stool examination was ordered because of the unexplained eosinophilia. The feces contained rhabditiform larvae of *S stercoralis* and ova of *Trichuris trichiura*. The patient was treated with 400 mg of thiabendazole twice daily for two days.

Many individuals infected with *S stercoralis* are asymptomatic. A parasitic infection was suspected in this child only after a routine blood cell count demonstrated the presence of an unexpected peripheral eosinophilia.

Case 5.—A female infant was hospitalized at 1 year and 3 months of age because of vomiting and diarrhea of three weeks' duration. There was a one-week history of abdominal distention. The stools were watery, green, foul-smelling, and numbered six to ten per day. On admission, the infant weighed 8.6 kg (between the third and tenth percentiles) and was 76 cm long (25th percentile). She had a moderately distended abdomen and 2+ pitting edema of the lower extremities. The hemoglobin level was 10.1 g/dl, and the hematocrit value 37%. The WBC count was 10,000/cu mm, with 34% neutrophils, 36% band forms, 3% eosinophils, 32% lymphocytes, and 4% monocytes. The total serum protein concentration was 3.6 g/dl, with an albumin level of 2.6 g/dl. Repeated urinalyses were negative for protein. Roentgenographic examination of the upper gastrointestinal tract showed thickened duodenal mucosal folds, mild dilation, and segmentation of the barium column. A stool culture was negative for enteric pathogens. Several stool specimens were guaiac positive. Microscopical examination of stool disclosed many rhabditiform larvae of *S stercoralis*. Four percent of an intravenously injected dose of chromated Cr 51 serum albumin was recovered in a 96-hour stool collection (normal, less than 1% of the administered dose).

The patient was treated with 200 mg of

thiabendazole twice daily for three days. When evaluated in the outpatient clinic one month after treatment, the infant was asymptomatic. The total serum protein concentration was 5.1 g/dl, with an albumin level of 3.9 g/dl. Her stool was negative for parasites. Stool specimens from two of four siblings contained rhabditiform larvae of *S stercoralis*. The family was poor and lived in a remote rural section of Clay County, Ky. The children defecated promiscuously on soil near the house. They did not wear shoes during the summer.

A protein-losing enteropathy characterized by excessive protein loss into the feces and hypoalbuminemia may develop in patients with large worm burdens.[17,18] This case also demonstrates that individuals with symptomatic strongyloidiasis may exhibit no peripheral eosinophilia.

COMMENT

Life Cycle of *Strongyloides stercoralis*

The parasitic form of *S stercoralis* is the adult female, which measures just over 2 mm in length and 40 to 50 μ in width.[19] Their normal habitat is the duodenum and the first part of the jejunum, although in very heavy infections worms may extend from the pyloric canal to the colon. The gravid female lives embedded within the intestinal mucosa, where it oviposits several dozen eggs per day. The embryonated eggs hatch almost immediately and release rhabditiform larvae that migrate to the intestinal lumen.

There are three life cycles that noninfective rhabditiform larvae may undergo. In the *direct cycle*, the larvae are excreted with the feces and develop directly into infective filariform larvae in warm, moist soil. An infection is initiated when filariform larvae penetrate skin, usually bare feet. They migrate to the lungs and break out of the pulmonary capillaries into the alveoli. They molt several times to become adolescent worms that ascend the respiratory tract to the pharynx, are swallowed, pass to the small intestine, and mature into adults. The time interval from penetration of skin by infective larvae to the development of ovipositing females is 17 to 28 days. In the second type of life cycle, the *indirect* or *free-living cycle*, rhabditiform larvae passed in feces develop in soil into mature males and females. After copulation and fertilization, the gravid females deposit eggs in soil and new rhabditiform larvae are produced. They may repeat the indirect life cycle or develop directly into infective filariform larvae. *Autoinfection* or *hyperinfection* is the third type of life cycle. Under circumstances that are not well understood, rhabditiform larvae mature into filariform larvae within the intestine of the host. These infective larvae may gain access to the mesenteric venules or lymphatics by penetrating the intestinal mucosa (internal autoinfection) or the perianal skin (external autoinfection). Autoinfection provides a mechanism by which a patient's worm burden can be replenished or increased even though the host may never again come in contact with contaminated soil.

Epidemiologic Study

Strongyloides stercoralis has a worldwide distribution.[20] The prevalence of infection varies inversely with socioeconomic level and is highest in warm, moist regions where sanitary practices are poor. Although not highly prevalent, strongyloidiasis is found throughout much of the United States (Table).[1,2,5,11,12,20,21] It is endemic in some rural areas of the South. High infection rates have also been encountered among residents at some institutions for the mentally retarded.[11]

This small nematode is primarily a parasite of man, although dogs, chimpanzees, and a few other mammals have been found to be naturally infected. Except in rare instances, lower animals are not thought to be important sources of human infection.[22] Most human infections are acquired outdoors when polluted soil-containing filariform larvae comes in contact with skin. In contrast, the spread of infection among children in homes for the retarded is primarily an indoor infection acquired via the buccal mucosa after the act of licking or sucking of fingers or objects contaminated with infective fecal material.

Clinical Features

Although many individuals infected with *S stercoralis* are asymptomatic, this parasite may produce a broad spectrum of clinical manifestations.[7-9,23-26] The most common symptom is intermittent abdominal pain of mild to severe intensity.[7,23,27] Although the location varies, in most instances it is found in the upper part of the abdomen, especially in the epigastrium. It has been variously described as a dull, gnawing ache, a burning sensation, or a cramp-like discomfort and may be exacerbated by food or alcohol. Pressure to the area of discomfort frequently elicits pain. Diarrhea is another common symptom. It may be intermittent, often alternating with constipation, or chronic and continuous. The stools are frequently watery and mucoid but may resemble pea soup,[7,23,27] or be pale, bulky, and malodorous.[28] Strongyloidiasis should be suspected when peptic ulcer like pain occurs in association with eosinophilia and intermittent or chronic diarrhea.[23] Anorexia, nausea, vomiting, flatulence, malaise, weakness, weight loss, and abdominal bloating are frequently reported.

Children with strongyloidiasis may have a celiac-like syndrome characterized by anorexia, irritability, chronic diarrhea, cachexia, retarded growth, abdominal distention, and steatorrhea.[8,27,29,30] Proof that infection with *S stercoralis* is causally associated with this malabsorption syndrome is established when the clinical findings are reversed following elimination of the parasite with appropriate therapy. Excessive loss of proteins into the intestine, hypoalbuminemia, and peripheral edema may develop in severe infections.[17,18,31]

The initial penetration of skin by filariform larvae produces no signs or symptoms; however, repeated infection may result in the development of a papular, pruritic, erythematous rash.[19] Autoinfection may cause a distinctive form of cutaneous larva migrans involving the buttocks, thighs, perineum, back, and abdomen, called larva currens.[32] The characteristics of this rash are its rapid movement, averaging 10 cm/hr; its typical

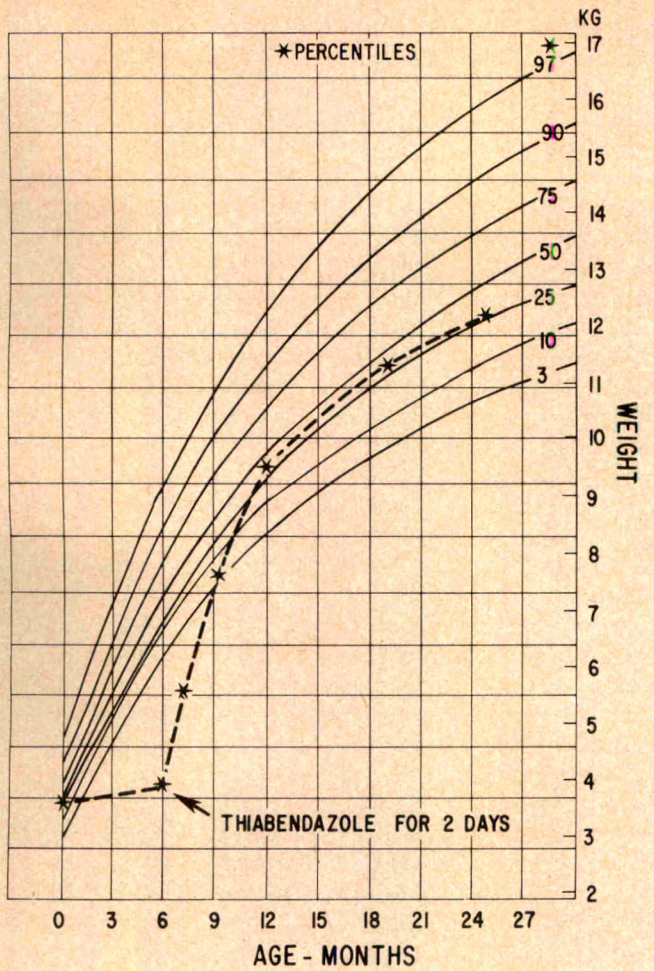


Fig 1.—Case 2. Prolonged growth failure in this infant was promptly reversed by thiabendazole therapy.

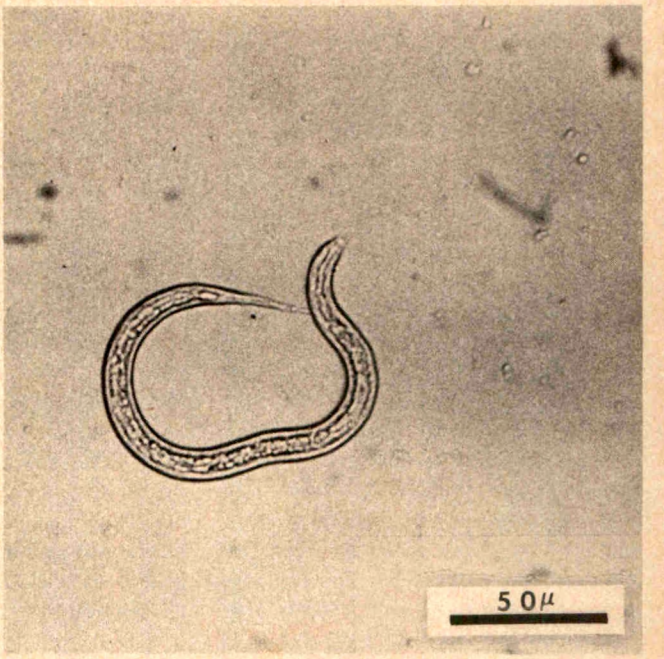


Fig 2.—Rhabditiform larva of *Strongloides stercoralis* from stool of patient with strongyloidiasis.

Recent Surveys of Prevalence of *Strongloides stercoralis* in the United States

State (City or County)	Source	Survey Year	No. of Patients Examined	% of Individuals Infected With *S stercoralis*	Comments
Kentucky Harlan County	Fulmer & Huempfner[1]	1963	125	4	Children from selected grades in several elementary schools
Louisiana New Orleans	Hubbard et al[21]	1972	8485	0.4	Charity hospital
New York Staten Island	Yoeli et al[11]	1970	2410	3.1	Willowbrook State School for mentally retarded patients
Brooklyn	Eveland et al[12]	1975*	10,072	1	King's County Hospital
Illinois Chicago	Winsberg et al[4]	1973	358	1.7	Survey of Latino residents
Tennessee Williamson County	Quinn[2]	1969	221	0.9	Children enrolled in Head Start

*Refers to year of publication because year of survey not stated.

distribution, with lesions starting within a 30-cm radius of the anal orifice; its tendency to recur for years if untreated; and the finding of rhabditiform larvae of *S stercoralis* in the patient's stool.[33]

Cough, wheezing, dyspnea, peripheral eosinophilia, and transient, migratory pulmonary infiltrates (Loeffler's syndrome) occasionally accompany the transpulmonary migration of larvae.[24,34-37] The pulmonary signs and symptoms are nonspecific, uncommon, and generally mild except in immunosuppressed patients with overwhelming infection.[10]

Massive hyperinfection usually occurs as an opportunistic infection when cell-mediated immunity is depressed as a result of disease (leukemia, lymphoma, protein calorie malnutrition, etc) or following the administration of immunosuppressant drugs, especially corticosteroids.[10] Severe abdominal pain is a common symptom. Nausea, vomiting, abdominal distention, abdominal tenderness,

weakness, and eosinopenia are also frequently reported.[38-40] The enteritis and/or colitis associated with a heavy infection may cause severe diarrhea, dehydration, serum electrolyte abnormalities, gastrointestinal protein loss, hypoproteinemia, edema, marked weight loss, anemia, paralytic ileus, and shock. That massive hyperinfection is in need of wider recognition is indicated by a review of 103 cases by Dwork et al[10]; despite the presence of marked symptoms, 47% of the patients were not suspected of having strongyloidiasis until autopsy. In fatal cases, death has been attributed to malnutrition, paralytic ileus, generalized peritonitis, and Gram-negative septicemia that may lead to pneumonia or meningitis.[6,40,41] In occasional cases, overwhelming pulmonary invasion causes diffuse bilateral bronchopneumonia, and respiratory failure and may overshadow the gastrointestinal manifestations.[35]

Many nonspecific laboratory abnormalities have been noted in strongyloidiasis. Moderate or marked peripheral eosinophilia and leukocytosis are present during the early stages of an infection.[19] Later, as an infection becomes chronic, an eosinophilia of about 10% is typical.[7,9,23,24] However, the eosinophil count is normal in some infected individuals,[19] and eosinophilia is uncommon in patients with massive hyperinfection.[10] Anemia is often present.[23] Markedly elevated levels of serum immunoglobulin E are common.[25] Malabsorption of fat,[42] D-xylose,[42] vitamin B_{12},[28] folic acid,[42] and iron[42] have been demonstrated in some patients. The stool frequently contains occult blood.[42]

The roentgenographic abnormalities are mainly limited to the lungs and the gastrointestinal tract.[43] When larvae pass through the lungs, patchy areas of infiltration resembling bronchopneumonia may be detected. The roentgenographic appearance of the small intestine in mild and subclinical cases is often normal. In moderately severe cases, abnormalities are usually seen in the duodenum and proximal jejunum and include dilation, thickening of the mucosal folds, and abnormal motility.[31,42-44] The transit time may be increased or decreased or there may be alternating areas of hypermotility and hypomotility. A delay in the passage of barium through the third portion of the duodenum with prominent reverse peristalsis is a common finding. Nodular intramural defects secondary to granuloma formation are occasionally seen.[43] In severe cases, there may be complete loss of the mucosal folds, prominent mucosal ulcerations, and a narrowed, rigid, pipestem-like duodenum and/or jejunum. These roentgenographic manifestations must be differentiated from Crohn's disease, tuberculosis, and intestinal lymphoma. Plain x-ray films of the abdomen in patients with acute symptoms and very severe disease may show small bowel dilation and air-fluid levels. These findings resemble those seen in mechanical obstruction of the small bowel and may prompt an exploratory laparotomy.[31] The colon is occasionally involved in patients with massive hyperinfection, and the roentgenographic findings resemble those seen with granulomatous colitis or idiopathic ulcerative colitis.[43,44]

Pathologic Features

In some patients with mild intestinal strongyloidiasis, peroral small intestinal biopsy specimens of duodenum or jejunum are normal.[28,45] In others, alterations of the small intestinal mucosa are found, such as stunted, swollen, or fused villi; prominent eosinophilic infiltration of the lamina propria; chronic inflammation of the mucosa with mononuclear cells; and increased epithelial mitoses in the crypts. The major pathological abnormalities in mild and severe infections are found in the duodenum and jejunum.[44]

DePaola et al[46] described three different forms of enteritis in fatal cases of strongyloidiasis. Catarrhal enteritis, the mildest lesion, is characterized by mucosal congestion and edema, increased mucus production, and a moderate mononuclear and eosinophilic infiltration of the lamina propria. Microulcerations and mucosal hemorrhage are seen in some cases. Parasitic invasion is limited to the intestinal crypts and mucosa. In edematous enteritis, a form of intermediate severity, the mucosa and submucosa are thickened by edema. The villi are broad and blunted and resemble those seen in tropical sprue. There is a mild inflammatory reaction in the lamina propria, and parasites are encountered in all layers of the intestinal wall. In ulcerative enteritis, the most severe form, the wall of the small intestine is thickened by edema and fibrosis. There are mucosal atrophy, macroscopic ulcerations, and a mixed inflammatory response; most of the inflammation is probably attributable to secondary bacterial invasion. Parasites are seen in all layers of the intestinal wall. All three forms of enteritis may be seen in the same patient in different regions of the intestine. The basic pathologic alteration in all types is thickening of the bowel wall secondary to edema or fibrosis or both.

In fatal cases of strongyloidiasis with massive hyperinfection, the jejunum, ileum, appendix, and colon may be extensively involved with an ulcerative enterocolitis.[10,44] Although eosinophilic infiltration is prominent in milder forms of strongyloidiasis, there is an absence of tissue and peripheral eosinophilia in most fatal cases. The inflammatory infiltrate is composed of lymphocytes, plasma cells, and neutrophils. Filariform larvae may be found in the mucosa, submucosa, muscularis, and serosa as well as the lymphatics, mesenteric nodes, mesenteric venules, and the liver. Invading viable larvae provoke little or no reaction; tubercle-like granulomas containing macrophages, lymphocytes, and foreign-body giant cells may be observed surrounding fragments of dead larvae. In some cases, colonic involvement is subtle and only detectable by microscopy.

The migration of filariform larvae from pulmonary capillaries into alveoli is accompanied by a variable amount of hemorrhage into the air spaces. The larvae are usually surrounded by neutrophils, erythrocytes, lymphocytes, desquamated epithelial cells, macrophages, and edema fluid. Massive hyperinfection is often associated with extensive larval migration in the lungs, widespread hemorrhagic pneumonia, and severe impairment of

pulmonary function to which may be added secondary bacterial infection. Occasionally, filariform larvae in the lungs gain access to the systemic circulation and are widely disseminated throughout the body, especially to the kidneys, brain, and heart.[38]

Diagnosis

The diagnosis of intestinal strongyloidiasis is made by identification of rhabditiform larvae in stool or duodenal fluid (Fig 2). The actively motile rhabditiform larvae measure 200 to 250 μ in length by 14 to 16 μ in width. They are readily distinguished from those of hookworm and the free-living rhabditis species by their short buccal chamber (approximately 4 μ in length), and by the presence of a conspicuous genital primordium that is midway between the esophagus and anus.[19] A diagnosis of autoinfection is occasionally made by recognizing the larger filariform larvae (about 700 μ in length) in the feces.[47]

The parasite is liable to be overlooked unless multiple stool specimens collected at 24- to 48-hour intervals are examined.[48-50] Jones and Abadie[7,49] found that a single stool specimen was positive in infected individuals only 27% of the time. Five or more stool examinations increased the yield to 80%. When the number of larvae in a stool specimen is small, the chance of discovery is increased if a concentration technique supplements the examination of direct fecal-saline smears.[48-50] Of the routine concentration methods, the formaldehyde-ether technique of Ritchie is recommended because zinc sulfate flotation is not very useful for diagnosis of strongyloidiasis.[9,50] Cultivation of stool on filter paper using the Haradi-Mori test tube technique makes it possible to recover larvae otherwise undetected with the 10% formaldehyde-ether concentration procedure in some patients with light infections.[50] The Haradi-Mori test tube cultivation procedure is simple to perform and requires no special equipment.[51] Probably the most efficient method for the recovery of strongyloides larvae in stool is Baermann's fecal extraction technique.[13,48] It provides a method for the concentration of larvae in a large volume of stool, and it is as effective as the evaluation of duodenal contents.[16] One disadvantage of Baermann's technique is that it is a cumbersome method ill adapted to routine use in the hospital laboratory.

In a suspected case, if the parasite cannot be found after a reasonable number of examinations of concentrated stool specimens, and especially if the Haradi-Mori test tube cultivation method and Baermann's extraction technique are not available, duodenal fluid should be evaluated. Most cases will be detected if the results of a duodenal aspirate and multiple stool examinations are combined.[7,49] A comparative study of the various techniques used to diagnose strongyloidiasis using duodenal contents has shown that microscopical examination of upper small intestinal contents obtained with a nylon yarn coiled inside a weighted gelatin capsule is superior to the evaluation of duodenal fluid obtained by intubation and aspiration.[14] Small intestinal biopsy is inferior to the evaluation of upper small intestinal contents for the diagnosis of strongyloidiasis.[44,45] If pulmonary manifestations are present, sputum and gastric aspirate should be examined.[52]

In our patients, we evaluated two direct fecal smears, one in physiologic saline and one in Lugol's iodine stain. In addition, a portion of each specimen was examined after it was concentrated by the formaldehyde-ether sedimentation technique. In a suspected case, if repeated examinations of concentrated stool specimens were negative, duodenal fluid or upper small intestinal contents were evaluated.

Treatment

All individuals harboring *S stercoralis* should be treated because of the pathogenic potential of the parasite. The drug of choice is thiabendazole, 25 mg/kg of body weight twice daily for two days.[26,53,54] Side effects frequently reported include anorexia, nausea, vomiting, and dizziness. Less common adverse effects are diarrhea, abdominal discomfort, pruritus, weariness, and headache. A single course of treatment may fail to eradicate the organism in 10% to 20% of cases.[25,53-55] In such instances, a second course of treatment is indicated and usually successful. In immunodeficient patients with massive hyperinfection, it may be difficult to eliminate the parasite.[10] Adam and colleagues[40] eradicated the parasite only after using the recommended daily dose of thiabendazole for at least two weeks. If thiabendazole is not tolerated, pyrvinium pamoate is an alternative drug with satisfactory cure rates.[55] The dose is 5 mg/kg of body weight per day in divided doses for seven days (maximum dosage, 250 mg/day). The drug is best given after meals to reduce the side effects of nausea and vomiting.

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Radiological Case of the Month

Lionel W. Young, MD; Contributed by Richard E. McClead, Jr, MD;
Martin Graham, MB, ChB; Barry D. Fletcher, MD

Clinical History.—A 2,290 g, 35-week preterm infant girl was transferred to Rainbow Babies and Children's Hospital, Cleveland, at 3 hours of age because of respiratory distress. The 30-year-old mother was gravida 3, para 1, abortus 1. Her pregnancy was uncomplicated until 35 weeks when a cesarean section was performed because of premature onset of labor complicated by breech presentation.

On admission, the infant was cyanotic in 60% oxygen. Examination of the chest showed an increased anteroposterior diameter, decreased chest excursion, intercostal retractions, and grunting respirations. The lungs were clear to auscultation. Examination of the heart was normal. The abdomen was soft with no distension, hepatosplenomegaly, or tenderness. The arterial blood gases in 65% fractional inspiratory oxygen (FIO_2) were a pH of 7.26, Pco_2 was 40 mm Hg, and Po_2 was 123 mm Hg. The initial chest roentgenogram is shown in Fig 1.

After obtaining cultures, antibiotics were begun. The infant subsequently required continuous distending pressure ventilation (CDPV) delivered via the nasal route. Because of deteriorating blood gases, she was intubated and placed on mechanical ventilation on the second day. With this mode of therapy, improvement was rapid. On the third day, blood cultures obtained at the time of admission were reported to be growing group B β-hemolytic streptococci. Despite improvement of blood gases and reduction of environmental oxygen from 100% to 40%, multiple attempts to wean the child from CDPV were unsuccessful. A follow-up chest roentgenogram (Fig 2) showed an unexpected finding.

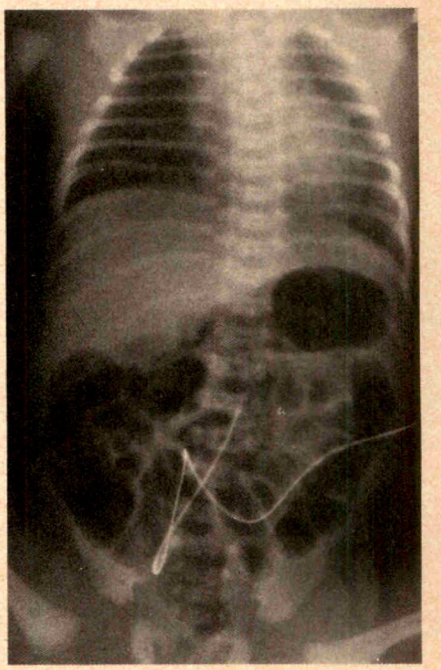


Fig 1.

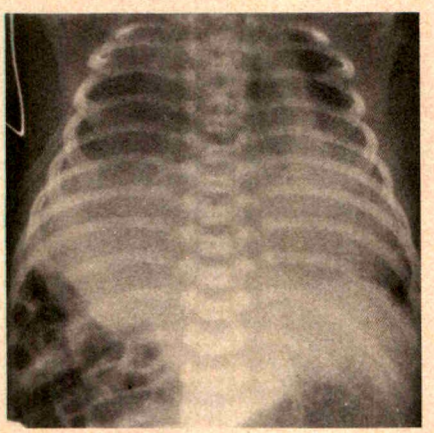


Fig 2.

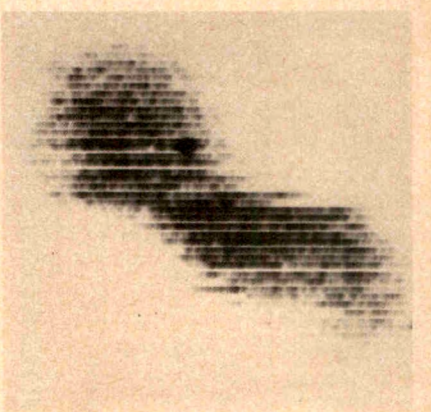


Fig 3.

From the Departments of Pediatrics (Drs McClead and Graham) and Radiology (Dr Fletcher), Rainbow Babies and Children's Hospital, University Hospitals of Cleveland and Case Western Reserve University.

Reprint requests to Department of Radiology, Children's Hospital of Pittsburgh, 125 DeSoto St, Pittsburgh, PA 15213 (Dr Young).

Denouement and Discussion

Postnatal Appearance of Diaphragmatic Hernia

Fig 1.—Anteroposterior roentgenogram of chest and abdomen on first day of life.

Fig 2.—Anteroposterior roentgenogram of chest, age 12 days.

Fig 3.—Liver-spleen scan made after injection of technetium Tc 99m sulfur colloid showed elevation of right lobe of liver consistent with intrathoracic herniation. Marker indicates xiphoid process of sternum.

The initial original roentgenogram of the chest and abdomen (Fig 1) showed a very mild, diffuse, bilateral, reticulogranular pattern compatible with hyaline membrane disease. The abdominal viscera were in normal position. However, the subsequent chest roentgenogram (Fig 2) showed opacification of the lower portion of the right hemithorax and shift of the mediastinal structures to the left. The well-inflated right lung was seen in the upper half of the right hemithorax and it extended across the anterior mediastinum into the left side of the chest. An important observation was the change in position of the bowel in the right upper abdominal quadrant. Its relationship to the inferior surface of the liver indicated cephalad migration of the liver into the chest. A technetium Tc 99m sulfur colloid scan of the liver and spleen confirmed the intrathoracic position of the liver (Fig 3). Differential diagnoses included eventration of the diaphragm, diaphragmatic hernia, and diaphragmatic paralysis. Eventration seemed unlikely because of the normal position of the right hemidiaphragm at birth; diaphragmatic paralysis was discarded because of absence of associated Erb's or facial palsy and a lack of history of birth trauma.[1] At operation, a large Bochdalek (posterolateral) diaphragmatic hernia was found and reduced successfully. The patient had an uneventful postoperative course.

Foramen of Bochdalek hernias usually cause considerable respiratory distress at birth and are usually present on roentgenograms in the immediate postnatal period. They are usually left-sided.[2] On the other hand, hernias through the foramen of Morgagni are usually right-sided and need not be present at birth, although they are commonly smaller than the hernia found in our patient.

Glasson et al[3] recently reviewed congenital posterolateral diaphragmatic hernias in children with previously normal chest roentgenographic findings. They report three cases and refer to an additional eight in the literature. Hurdiss et al[4] have described a 12th case. Of these patients, five had left-sided hernias and seven had them on the right side.

Presumably, the abdominal organs, ie, liver or spleen, may occlude the hernial defect until the gradient between intra-abdominal and intrathoracic pressures can no longer be resisted, at which time, the abdominal contents herniate into the thorax. We would speculate that the child's initial roentgenograms continued to be normal because of adequate pulmonary inflation due to assistance with CDPV. With resolution of her alveolar atelectasis (presumptive hyaline membrane disease) and reduction of CDP, the liver was then able to herniate into the right side of the chest cavity.

Appropriate surgical intervention in these patients should provide normal pulmonary function since normal fetal lung growth and development are expected in the absence of an intrathoracic hernial mass in utero.

This case is a reminder that previously normal roentgenographic findings do not exclude the possibility of neonatal diaphragmatic hernia.

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The Editors welcome contributions to "Picture of the Month" and "Radiological Case of the Month." Those who wish to contribute should send their manuscripts to Dr Gellis (Picture of the Month), Boston Floating Hospital, 20 Ash St, Boston, MA 02111, or Dr Young (Radiological Case of the Month), Department of Radiology, Children's Hospital of Pittsburgh, 125 DeSoto St, Pittsburgh, PA 15213. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.

Congenital Mesoblastic Nephroma

The clinical findings of an upper abdominal mass, abdominal bruit, and congestive heart failure in a neonate invariably suggest a diagnosis of hemangioma of the liver. Abnormal arteriovenous communications have rarely been described in other abdominal tumors.[1] We have recently had the opportunity to care for an infant with a congenital mesoblastic nephroma who developed congestive heart failure during the first 12 hours of life. An arteriovenous shunt through the highly vascular renal tumor appeared to play an important role in the pathogenesis of this patient's cardiac decompensation.

Report of a Case.—A 2,960-g male infant was born to a gravida 3, para 2, abortus 0 mother following a 35-week gestation complicated by polyhydramnios. Apgar scores at one and five minutes were 6 and 9, respectively. Pulse rate was 158 beats per minute; respirations, 48/min. There was no cyanosis or grunting. On the initial physical examination, a large right upper quadrant abdominal and flank mass was noted. The liver edge could not be clearly distinguished from the mass. The tumor did not transilluminate.

Roentgenograms demonstrated moderate cardiac enlargement with increased pulmonary vascularity, and an abnormal soft tissue density in the right upper quadrant. Intravenous pyelography disclosed a normal left kidney, ureter, and bladder. The right kidney was displaced inferiorly, and the pelvocalyceal system was markedly distorted by a mass at the upper pole. Abdominal sonography defined the solid nature of the lesion, but failed to clearly distinguish the organ of origin.

Twelve hours after birth, the infant developed evidence of cardiac decompensation. Tachypnea (respirations, 88/min) and tachycardia (pulse rate, 168 beats per minute) were noted. The blood pressure was 86/42 mm Hg. There was no cyanosis. A soft continuous bruit was audible over the abdominal mass. A grade 3/6 systolic murmur that radiated to the left scapular area was present at the left sternal border. Peripheral pulses were prominent. Repeated chest roentgenograms demonstrated an increase in the pulmonary vascularity and greater cardiac enlargement. The cardiothoracic ratio was 0.7. The infant responded rapidly to the administration of digitalis, diuretics and oxygen.

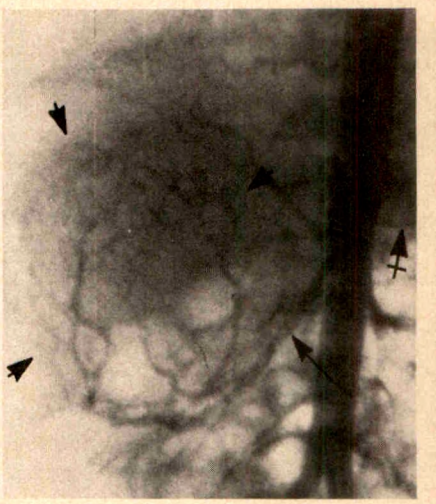
On the second day of life, a transumbilical abdominal aortogram was obtained. The right renal artery was very large and deviated inferiorly. It supplied a 6-cm vascular mass in the upper pole of the right kidney (Figure). The hepatic arterial supply was normal. Because of the persistence of mild congestive heart failure and the precordial and abdominal bruits, cardiac catheterization was performed; it showed a left-to-right shunt at the level of the right kidney and a small patent ductus arteriosus (Table).

At surgery, a 6-cm vascular mass was found to be arising from the upper pole of the right kidney, with no evidence of local invasion or intraabdominal metastasis. A right nephroureterectomy was performed. The precordial murmur disappeared during the immediate postoperative period. Recovery was uneventful and the infant was discharged to home on the sixth postoperative day. Digitalis was discontinued prior to discharge. There has been no further evidence of a cardiac murmur or of congestive heart failure.

The kidney weighed 96 g. Approximately 80% of the renal parenchyma was replaced by a circumscribed, firm, white tumor 5.5 cm in diameter. The cut surface was trabeculated and glistening. On histologic examination, there was a transition from normal renal tissue into a solid mass composed of interweaving bands of fibromyomatous stroma. Within the tumor there were large abnormal vascular spaces lined with endothelium.

Comment.—In this infant, severe cardiac decompensation 12 hours after delivery was a cause for grave concern. There were several factors that theoretically allowed this patient to progress so rapidly into congestive heart failure: (1) prematurity, (2) arteriovenous shunting, and (3) a patent ductus arteriosus. The pulmonary arteries of premature infants have relatively thin medial muscular coats.[2] This results in a very rapid decrease in pulmonary vascular resistance and increased right-sided cardiac pressures shortly after birth, and there is frequently a large left-to-right shunt through a patent ductus arteriosus.[3-5]

Systemic arteriovenous fistulae in infants in utero act as a site of low peripheral resistance similar to the placenta. The two areas combine to cause an increase in the fetal cardiac output, resulting in a hyperdynamic state with cardiomegaly and decreased cardiac compliance.[6] Thus, at birth, this premature infant who already had a compromised myocar-



Arterial phase film of umbilical aortogram demonstrates enlargement and inferior displacement of right renal artery (long arrow), which supplies hypervascular upper pole renal mass with irregular vascular spaces (short arrows). Left renal artery (crossed arrow) is normal.

Cardiac Catheterization Data

Site	Oxygen Saturation, %	Pressure, mm Hg
Inferior vena cava (low)	76	. . .
Right renal vein	89	. . .
Left renal vein	80	. . .
Inferior vena cava (high)	88	. . .
Superior vena cava	79	. . .
Right atrium	86	$\bar{4}$*
Right ventricle	83	30/6
Main pulmonary artery	84	30/10, $\bar{14}$
Left pulmonary artery	84	30/10, $\bar{14}$
Aorta (via ductus)	97	120/55, $\bar{65}$
Left atrium	. . .	$\bar{4}$
Left ventricle	98	120/10
Cardiac index, liters/min/sq m	4.2	
Total systemic vascular resistance, dyne sec cm^{-5}	1,733	
Total pulmonary vascular resistance, dyne sec cm^{-5}	267	

*Bar indicates mean pressure in each chamber or vessel.

dium was confronted with a volume load through both the arteriovenous fistula and the patent ductus arteriosus. Because of the arteriovenous shunt, the blood on the right side of the cardiac circuit had an increased oxygen content, which further dilated the pulmonary vascular bed. Under these conditions, the baby rapidly overloaded his pulmonary circuit and subsequently his left heart, resulting in severe early biventricular congestive heart failure.

Congenital mesoblastic nephroma is a relatively rare tumor whose clinical and histologic characteristics have only recently been emphasized in the literature.[7] Bolande states: "Histologically, the tumor is composed of tightly interlaced sheets and bundles of immature connective tissue cells.... Irregularly distributed throughout this tissue are large, tortuous vascular spaces.... Focal clustering of such vascular structures may give the impression of an angiomatous or lymphangiomatous malformation."[7] In our patient, both the histologic characteristics and the angiographic findings suggested the presence of an angiomatous component within the tumor. The catheterization data, which demonstrated a large step-up in oxygen content in the right renal vein and vena cava, confirmed the significance of this child's neoplasm as a functional arteriovenous shunt.

Arteriovenous shunting in renal tumors is distinctly unusual during the neonatal period.[8] To our knowledge, this has not been previously described in a patient with congenital mesoblastic nephroma. Such tumors frequently display angiomatous elements, however, and it is suggested that this aspect of the clinical presentation may have been overlooked in some patients. Although emergency surgery for control of congestive heart failure was not required in our patient, cardiac decompensation secondary to arteriovenous shunting could be an indication for urgent surgical intervention in others.

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Intussusception in a 14-Year-Old Boy Secondary to an Intramural Fecalith

Intussusception in an adolescent population is an unusual occurrence. Published reviews of intussusception in infancy and childhood have consistently indicated a 60% to 90% occurrence rate in children younger than 2 years of age.[1] To our knowledge, an intramural fecalith as a lead point for intussusception has not previously been reported in the major reviews of this entity.

Report of a Case.—A 14-year-old boy was admitted for evaluation of intermittent acute abdominal pain of nine to ten days' duration. He had had an appendectomy at the age of 3 years. His father was listed as missing in action (MIA), and the boy had been under psychiatric care from age 7 to age 10 because of difficulties arising from this situation.

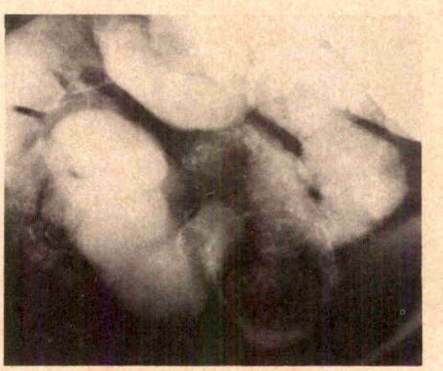
He developed acute abdominal pain associated with one episode of emesis three days after the government announced that no MIAs were considered to be alive. He was evaluated at that time and examination proved unremarkable. He was given a clear liquid diet and the pain subsided. Three days later, there was recurrence of severe cramping lower abdominal pain. No fever, emesis, hematochezia, or diarrhea was present. Examination at this time disclosed tenderness over the appendiceal scar region. Questionable rebound tenderness was elicited. The CBC count, ESR, and urinalysis were normal. Pain subsided over the next few hours, and again the boy was asymptomatic for the next three days. Pain recurred and a barium enema was performed. It showed a large filling defect in the cecum with a "coiled spring" appearance typical of intussusception (Figure). It could be only partially reduced; under fluoroscopy, there appeared to be a mass in the area of the appendiceal stump acting as a lead point for the colocolonic intussusception.

Because of the possibility that the cecal mass represented a malignant tumor, the bowel was prepared, and a right hemicolectomy consisting of the terminal ileum, cecum, and ascending colon was performed. Pathological examination showed a 4-cm mass almost filling the entire cecum. This mass consisted of a fecalith in a cavity communicating with the lumen of the cecum via a 1-cm lumen. The cavity was lined by intestinal mucosa on both sides. It is postulated that this cavity was in some way related to the previous appendectomy. The lumen was in the area of, and about the same size as, the normal orifice of the appendix. Somehow, this must have regained patency and allowed fecal material to enter and become trapped in the cavity, thus giving rise to the fecalith.

Comment.—The history and physical findings in intussusception in infants are well known. In older children, this classical picture is often lacking. The condition tends to be much less acute and therefore adds to the confusion concerning diagnosis.[1]

In children over 3 years of age, 11% of intussusceptions were caused by specific lesions.[2] Polyps, duplications, Henoch-Schonlein purpura, suture line, appendix, and Meckel's diverticulum all act as lead points. An enterogenous cyst and two cases of enteric cysts acting as lead points have been reported.[3,4] To our knowledge, however, a large fecalith in an intramural cyst has not caused this problem previously. Lymphosarcoma is also a possibility[3,4] and is the commonest malignant tumor at this site in children.

The knowledge of this association of



Barium enema shows typical "coiled spring" appearance of intussusception, with suggestion of mass lesion at lead point.

lymphosarcoma as a lead point in intussusception in an older child played a major role in recommending a hemicolectomy in the case presented. It was gratifying, however, to find a fecalith as the "mass" in this boy's cecum.

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Solitary Pyogenic Liver Abscess in Children

Pyogenic liver abscesses are infrequent in pediatric patients, although they are said to occur in debilitated children[1] and in children with chronic granulomatous disease.[2] We report here five cases of pyogenic liver abscess in previously healthy children, diagnosed in a period of nine months at the Hospital de Criança Conceição, Porto Alegre, Brazil.

Report of Cases.—CASE 1.—A 4-year-old boy with fever, lassitude, weight loss, and an upper respiratory tract infection of ten days' duration was admitted with mild abdominal distention and tender hepatomegaly (liver edge 9 cm below right costal margin). The chest roentgenogram showed a right lower lobe consolidation. The hemoglobin level was 8 g/dl; the WBC count, 12,000/cu mm, with rare myelocytes, 54% band cells, 26% segmented neutrophils, 5% eosinophils, and 14% lymphocytes. Serum transaminase levels were slightly altered: SGOT, 50 Sigma Frankel units (normal 8 to 40); SGPT 51 Sigma Frankel units (normal, 5 to 35); serum bilirubin level was normal. A sickle cell preparation was negative, and an intravenous pyelogram was normal.

He received penicillin G intravenously for the pneumonia, but on the sixth hospital day was prostrated with fever (temperature 38 °C) and had increasing pain over the area of the liver. A liver scan with technetium Tc 99m showed a 7-cm area of decreased uptake in the posterolateral portion of the right lobe. This area also showed decreased uptake following intravenous radionucleotide perfusion hepatography with indium 113m. The liver abscess was drained. He received ampicillin and gentamicin for five days, then penicillin and dicloxacillin when *Staphylococcus aureus* was isolated from cultures of blood and the liver aspirate. He had an uneventful recovery, with fever lasting for 12 days. The liver scan on the 20th day after the drainage showed a clear diminution of the abscess area.

CASE 2.—A 10-year-old girl, who reported trauma to the right hemithorax five days earlier, was admitted with generalized urticaria, chest pain, fever, and diarrhea. The right upper quadrant was tender to palpation, and the liver edge was 5 cm below the right costal margin. The chest roentgenogram showed consolidation of the right lower lobe and elevation of the right hemidiaphragm. There was no evidence of rib fracture. The plain abdominal roentgenogram suggested hepatosplenomegaly. The hemoglobin level was 10.2 g/dl; the WBC count, 12,000/cu mm, with 1% juvenile neutrophils, 31% band cells, 54% segmented neutrophils, 1% eosinophils, and 8% lymphocytes. The serum transaminase, bilirubin, and alkaline phosphatase levels were normal. The CSF was normal. The Widal test, Mantoux test, mononucleosis spot test, and blood cultures were negative.

She received adrenalin plus diphenhydramine on admission. Chloramphenicol was administered intravenously because of a history of penicillin allergy. Four days later, she remained febrile and had persistent right upper quadrant tenderness. The liver scan (Figure) and radionucleotide perfusion hepatography showed an 8-cm area of decreased uptake in the lower portion of the right lobe and poor perfusion. Surgical drainage of the abscess was performed and *S aureus* was isolated from the purulent exudate. She remained febrile for two weeks, but had an uneventful recovery.

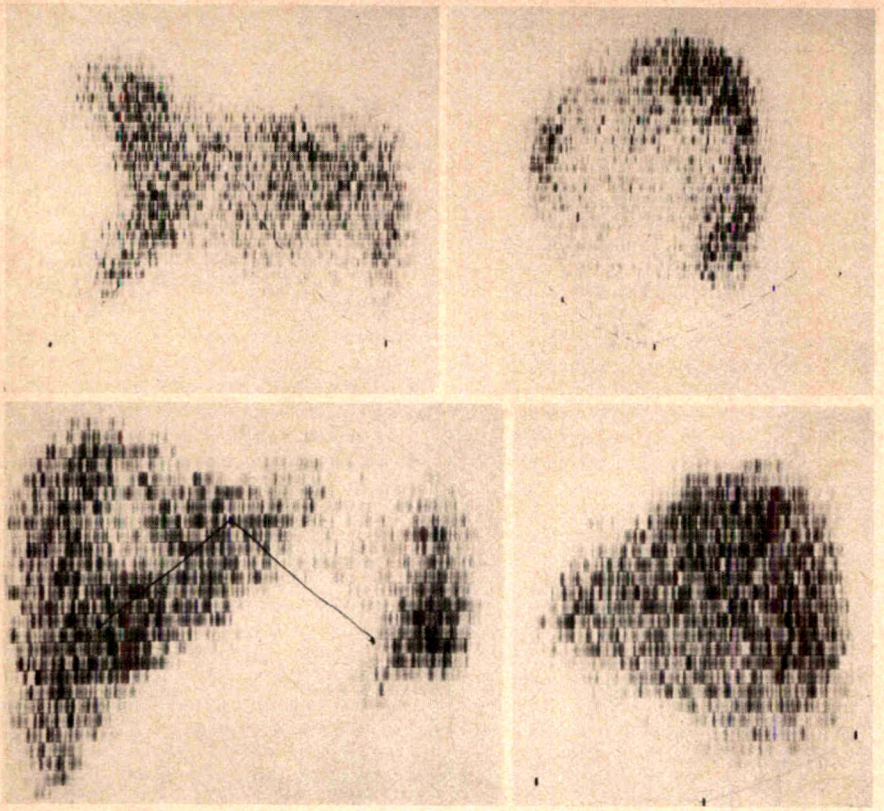
CASE 3.—A 5-year-old boy was admitted with diarrhea, vomiting, abdominal pain, and a high fever of three days' duration. He had dyspnea but no palpable hepatomegaly. The chest roentgenogram showed consolidation in the lower portions of both lungs. The plain abdominal roentgenogram was normal. The hemoglobin level was 10.4 g/dl; the WBC count, 9,000/cu mm, with 1% myelocytes, 2% juvenile neutrophils, 27% band cells, 46% segmented neutrophils, 3% eosinophils, and 17% lymphocytes. Serum transaminase and alkaline phosphatase levels were normal. The Widal test was negative. The CSF was normal. He received ampicillin intravenously but by the fifth hospital day his condition had not improved. Repeated roentgenograms showed pneumatoceles in both lungs and hepatomegaly. A liver scan (Figure) and radionucleotide perfusion hepatography showed a 3-cm area of decreased uptake in the upper portion of the liver, close to the interlobar fissure. The antibiotic was changed to chloramphenicol. Blood cultures on three occasions were negative. On the 23rd day after the diagnosis, a liver scan was normal. Recovery was uneventful.

CASE 4.—A 7-year-old boy was admitted with fever and abdominal pain of four days' duration. He had suffered abdominal trauma in a soccer game one week prior to admission. He was irritable and the parents reported a change in his behavior. The CSF was normal. The chest roentgenogram was normal and the plain abdominal roentgenogram suggested hepatomegaly. The hemoglobin level was 11.4 g/dl; the WBC count, 10,000/cu mm, with 1% myelocytes, 1% juvenile neutrophils, 31% band cells, 56% segmented neutrophils, 4% eosinophils, and 7% lymphocytes. Serum transaminase, alkaline phosphatase, bilirubin, BUN, and serum creatinine levels all were normal. Three days after admission, he became prostrated and the abdominal pain was more prominent in the right upper quadrant (liver edge 4 cm below right costal margin). The liver scan and radionucleotide perfusion hepatography showed a 4-cm area of decreased uptake in the lower portion of the right lobe. He received chloramphenicol and surgical drainage was performed. *Staphylococcus aureus* was isolated from the purulent material and from the blood. He remained febrile for ten days, but by the third week was doing well. The liver scan showed a clear diminution of the abscess area.

CASE 5.—A 9-year-old boy had fever and vomiting of ten days' duration. The right hypochondrium was tender to palpation. The hepatic edge was palpable 3 cm below the right costal margin. Roentgenogram of the chest and abdomen were normal. The hemoglobin level was 9 g/dl; the WBC count, 12,000/cu mm, with 12% band cells, 61% segmented neutrophils, 2% eosinophils, 2% monocytes, and 23% lymphocytes. Serum transaminase, alkaline phosphatase, and bilirubin levels were normal. Urine culture was negative. The liver scan and radionucleotide perfusion hepatography showed an area of decreased uptake 6 cm in diameter in the anterosuperior portion of the right lobe. Penicillin G and dicloxacillin were administered intravenously, and the abscess was surgically drained. Three blood cultures and bacteriologic culture of the purulent material were negative. He received antibiotics for 28 days, after which the liver scan showed a clear decrease in size of the abscess.

Comment.—The clinical diagnosis of a liver abscess is not easy and, according to Young,[3] the later the diagnosis the higher the mortality. In the autopsies reviewed by Dehner and Kissane,[1] only two of 27 cases were diagnosed during life.

The symptoms in the early stages are general and may not involve the liver area. The most common symptoms and signs are high fever, which may be of unknown origin,[4,5] and abdominal pain, initially diffuse and later becoming gradually localized to the right hypochondrium. Chills, nau-



Anterior and right lateral technetium Tc 99m liver scans of two cases. Top left, Case 2. Anterior scan shows decreased uptake along right lateral margin. Top right, Case 2. Right lateral scan shows large area of decreased uptake. Bottom left, Case 3. Anterior scan shows decreased uptake at level of interlobar fissure. Bottom right, Case 3. Right lateral scan.

sea, vomiting, diarrhea, weight loss, and anorexia are frequent complaints. Symptoms of respiratory infection are not uncommon; three of our five patients had pneumonia. Central nervous system alterations may occur (case 4) and could possibly be related to septic microemboli or toxins.

Hepatomegaly is not frequent at the beginning, but almost always occurs later with liver tenderness. Our cases confirm previous observations of normal liver function tests and the absence of jaundice despite the large size of the abscess. The appearance of jaundice is a bad prognostic sign because it may signal compression of the bile duct.

Splenomegaly is common. Leukocytosis with a shift to the left was found in all of our cases. Positive blood cultures were found in two of our five cases. Our cases suggest that a common cause of liver abscess in children is *S aureus*. This is in contrast with adults, in whom the Gram-negative bacteria are most common.

A liver scan is the most useful diagnostic test. It will show regions with poor vascularization greater than 2 cm in diameter as areas of poor uptake. The radioisotopes usually utilized are technetium Tc 99m, indium 113m, gold Au 198m, and gallium 67.[6,7] Of the five cases reported here, all had abnormal liver scans and four had surgical confirmation of the clinical diagnosis.

In our cases, the presence of tender hepatomegaly, a pyogenic focus (pneumonia), and/or occurrence of previous blunt trauma to the liver area are in agreement with the classical descriptions of pyogenic liver abscess.[8,9]

It is likely that this entity is more common than previously described in children. The occurrence of fever, hepatomegaly, right upper quadrant pain, and abdominal tenderness, with a history of abdominal trauma and lower lobe pneumonia, should lead the physician to consider a liver abscess.

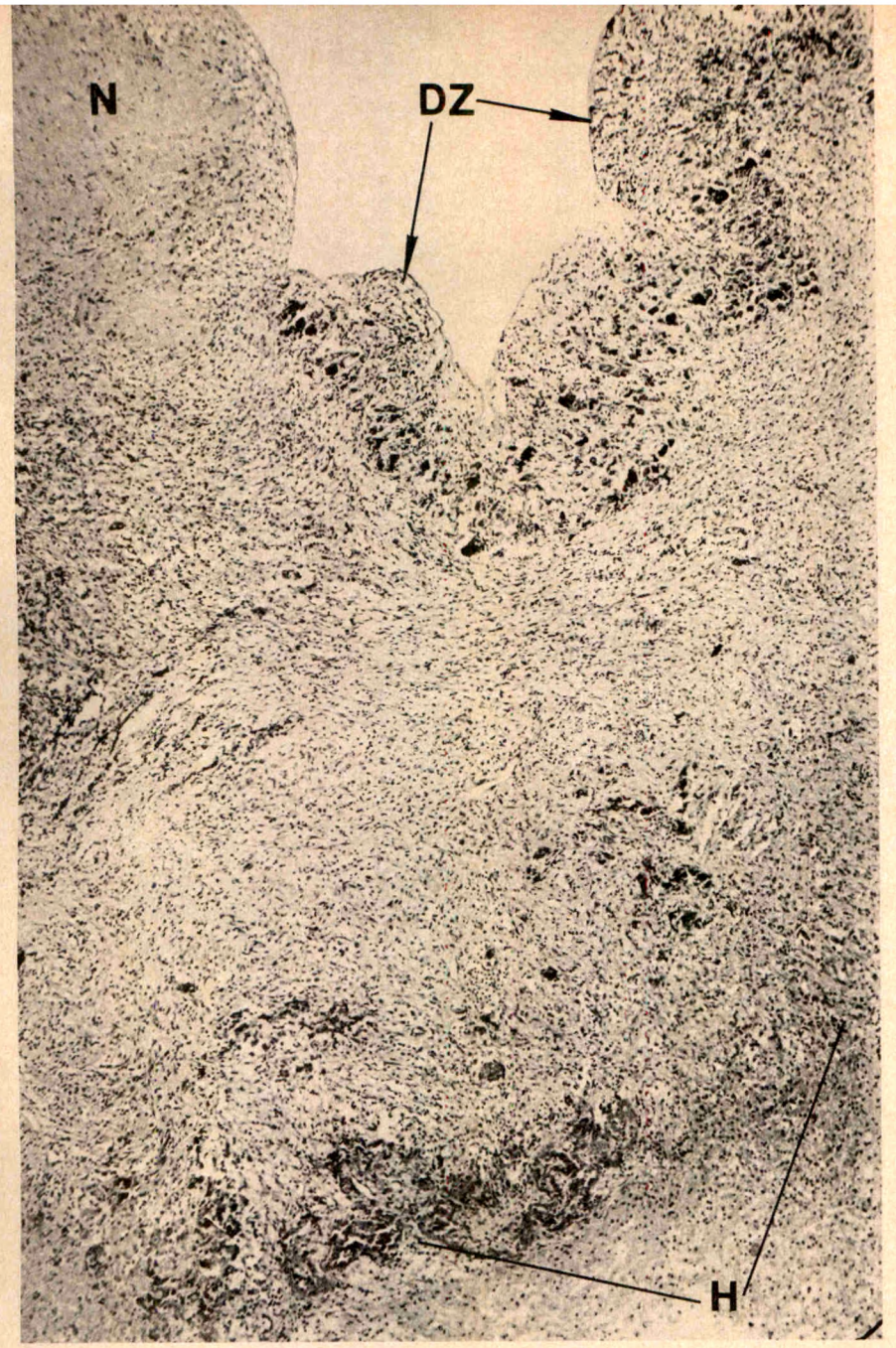
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Adrenal Hemorrhage in a Newborn With Beckwith-Wiedemann Syndrome

Two patients with Beckwith-Wiedemann syndrome have recently been reported[1] with adrenal calcifications that were presumed to be a consequence of unrecognized adrenal hemorrhage. We describe a patient with Beckwith-Wiedemann syndrome in the neonatal period with a massive hemorrhage of the right adrenal gland. To our knowledge, no other cases of confirmed bleeding into the adrenals have been reported in patients with this syndrome.

Report of a Case.—A male infant born after normal labor, with a birth weight of 3.7 kg, was transferred to the University of Pavia (Italy) Pediatric Department on the first day of life because of intense cyanosis, tachypnea, and macroglossia. On admission, an umbilical hernia, ear lobe anomaly, and hemihypertrophy were noted. The liver was palpable 3 cm below the right costal margin, and two round masses, thought to be enlarged kidneys, were palpable in each flank. A grade 3/6 systolic murmur was present. Laboratory data showed only hypoglycemia, partially corrected by frequent feedings and continuous intravenous infusion with 15% glucose solution. On the second day of life, the baby became jaundiced; despite phototherapy and phenobarbital, the serum bilirubin level rose to 22 mg/dl (indirect, 21 mg/dl) by the 16th hour of life. Hemoglobin level was 18.4 g/dl; hematocrit value, 53.8%; platelets, 150,000/cu mm; BUN level, 25 mg/dl; coagulation studies and serum thyroxine level were normal. There was no blood group incompatibility; Coombs' test



Layer of adrenal definitive zone (DZ) and intense fibrosis surrounding central hemorrhage (H). Provisional cortex is completely destroyed. Foci of coagulative necrosis are evident (N). Dark areas represent calcifications and hemosiderin deposition.

was negative, as were tests for glucose-6-phosphate dehydrogenase and pyruvate kinase deficiency. An exchange transfusion was performed. A second exchange transfusion became necessary on the fourth day (total serum bilirubin level, 24.8 mg/dl) and a third on the sixth day of life. On the 18th day, the icterus had finally disappeared, while the hypoglycemia was still present. Therapy with methylprednisolone was instituted; within five days, the blood glucose level reached normal values. Normal glucose levels persisted after discontinuation of therapy ten days later.

A chest roentgenogram and an ECG showed enlargement of the heart and biventricular hypertrophy. An intravenous pyelogram at age 20 days showed the right kidney to be displaced downward and rotated outward, with flattening of the upper calyces. The left kidney was large, but morphology and dye excretion were normal. Vanillylmandelic acid concentration in the urine was normal. A laparotomy, performed on the 53rd day of life, showed a large hemorrhagic cyst (5 cm in diameter) involving the right adrenal gland.

Histological examination of the surgically removed cyst (Figure) showed complete destruction of the provisional cortex by a massive hemorrhage. A peripheral layer of surviving definitive zone was still recognizable. In the inner layers of the cystic wall, scattered recent hemorrhages, areas of scar tissue laden with hemosiderin, dystrophic calcifications, and areas of coagulative necrosis were detected.

Recovery was uneventful, and ten months later the patient was well.

Comment.—Our case shows that adrenal hemorrhage in the neonatal period may occur in infants with Beckwith-Wiedemann syndrome. Predisposing factors are believed to be macrosomia and traumatic delivery, coagulation defects, hypoxia, and infection.[2] In our patient, only hypoxia was present at birth, possibly secondary to macroglossia.

Hyperbilirubinemia, which was particularly marked in our patient, has been attributed to reabsorption of blood and is a frequent finding in the Beckwith-Wiedemann syndrome. Black and Williams[2] state that marked hypoglycemia is often the only symptom of adrenal insufficiency following massive adrenal hemorrhage. The origin of hypoglycemia, which is present in 33% to 50% of patients with Beckwith-Wiedemann syndrome,[3] has been attributed solely to hyperinsulinism.[4]

In light of our observations, we would suggest that adrenal insufficiency be taken into account as an additional cause. An adrenal origin of the neonatal hypoglycemia should be considered when rapid correction of blood glucose levels is obtained with cortisone.

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Hepatic dysfunction with or without jaundice has occurred, chiefly in adults, in association with erythromycin estolate administration.

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Hepatic dysfunction with or without jaundice has occurred, chiefly in adults, in association with erythromycin estolate administration. It may be accompanied by malaise, nausea, vomiting, abdominal colic, and fever. In some instances, severe abdominal pain may simulate an abdominal surgical emergency.

If the above findings occur, discontinue Ilosone promptly.

Ilosone is contraindicated for patients with a known history of sensitivity to this drug and for those with preexisting liver disease.

Indications: Included among the indications for this drug is *Streptococcus pyogenes* (Group A Beta-Hemolytic)—Upper and lower respiratory tract, skin, and soft-tissue infections of mild to moderate severity.

Injectable penicillin G benzathine is considered by the American Heart Association to be the drug of choice in the treatment and prevention of streptococcal pharyngitis and in long-term prophylaxis of rheumatic fever.

When oral medication is preferred for treating the above-mentioned conditions, penicillin G or V or erythromycin is the alternate drug of choice.

The importance of the patient's strict adherence to the prescribed dosage regimen must be stressed when oral medication is given. A therapeutic dose should be administered for at least ten days.

Consult the package literature for other indications.

Contraindication: Known hypersensitivity to this antibiotic

Warnings: (*See* Warning box above.) The administration of erythromycin estolate has been associated with the infrequent occurrence of cholestatic hepatitis. Laboratory findings have been characterized by abnormal hepatic function test values, peripheral eosinophilia, and leukocytosis. Symptoms may include malaise, nausea, vomiting, abdominal cramps, and fever. Jaundice may or may not be present. In some instances, severe abdominal pain may simulate the pain of biliary colic, pancreatitis, perforated ulcer, or an acute abdominal surgical problem. In other instances, clinical symptoms and results of liver function tests have resembled findings in extrahepatic obstructive jaundice.

Initial symptoms have developed in some cases after a few days of treatment but generally have followed one or two weeks of continuous therapy. Symptoms reappear promptly, usually within 48 hours after the drug is readministered to sensitive patients. The syndrome seems to result from a form of sensitization, occurs chiefly in adults, and has been reversible when medication is discontinued.

Usage in Pregnancy—Safety of this drug for use during pregnancy has not been established.

Precautions: Caution should be exercised in administering the antibiotic to patients with impaired hepatic function.

Surgical procedures should be performed when indicated.

Adverse Reactions: The most frequent side effects are gastrointestinal (e.g., abdominal cramping and discomfort) and are dose related. Nausea, vomiting, and diarrhea occur infrequently with usual oral doses.

During prolonged or repeated therapy, there is a possibility of overgrowth of nonsusceptible bacteria or fungi. If such infections arise, the drug should be discontinued and appropriate therapy instituted.

Mild allergic reactions, such as urticaria and other skin rashes, have occurred. Serious allergic reactions, including anaphylaxis, have been reported.

Administration and Dosage: *Adults*—The usual dosage is 250 mg every six hours. This may be increased up to 4 gm or more per day according to the severity of the infection.

Children—Age, weight, and severity of the infection are important factors in determining the proper dosage. The usual regimen is 30 to 50 mg per kg per day in divided doses. For more severe infections, this dosage may be doubled.

If administration is desired on a twice-a-day schedule in either adults or children, one-half of the total daily dose may be given every 12 hours.

Streptococcal Infections—For the treatment of streptococcal pharyngitis and tonsillitis, the usual dosage range is 20 to 50 mg per kg per day in divided doses.

Body Weight	Total Daily Dose
10 kg or less (less than 25 lb)	250 mg
11-18 kg (25-40 lb)	375 mg
18-25 kg (40-55 lb)	500 mg
25-36 kg (55-80 lb)	750 mg
36 kg or more (more than 80 lb)	1000 mg (adult dose)

In the treatment of group A beta-hemolytic streptococcal infections, a therapeutic dosage of erythromycin should be administered for at least ten days. In continuous prophylaxis of streptococcal infections in persons with a history of rheumatic heart disease, the dosage is 250 mg twice a day.

Consult the package literature for further dosage information.

[060278]

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Letters to the Editor

Subdural Empyema

Sir.—We were interested in the report of subdural empyema in an infant due to group B β-hemolytic streptococcus as presented by Drs Ferguson and Gotoff in the CLINICAL MEMORANDA section of the January issue of the JOURNAL (131:97, 1977). We would like to correct their statement that this infection has not been previously reported. In the September 1976 issue of the JOURNAL (130:1003-1004, 1976), we described an infant with group B streptococcus meningitis and otitis media. As we described in that article, the infant was found to have bilateral subdural empyema, which was managed by aspiration of the subdural space bilaterally. Group B streptococci were isolated from the fluid. As mentioned, the subdural aspirates were not productive by the fifth hospital day.

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T_3 Thyrotoxicosis

Sir.—Reporting a case of T_3 thyrotoxicosis in a child, Weiss et al (132:374-375, 1978) postulated that in pediatric patients the disease may be more common than indicated by the few reported cases.

We have had the opportunity to study a T_3 toxicosis in a 10-year-old girl with diffuse goiter and exophthalmus. Thyroid studies showed normal serum thyroxine (T_4) level, raised serum triiodothyronine (T_3) level, raised uptake of radioactive iodine by thyroid, and absence of serum thyroid-stimulating hormone response to thyrotrophin-releasing hormone.[1] In spite of the fact that both low or high iodide ingestion have been reported as an etiologic factor in some cases of T_3 thyrotoxicosis, a detailed dietary history did not disclose data to support such an etiology in our patient. Poor iodination of thyroglobulin,[2] interference in the peripherical conversion of T_4 to T_3,[3] or the presence of thyroid-stimulating immunoglobulins[4] may be alternative factors to explain the increased T_3 serum levels.

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3. Chopra IJ: An assessment of daily production and significance of thyroidal secretion of 3,3′,5′-triiodothyronine (reverse T_3) in man. *J Clin Invest* 58:32, 1976.
4. Hall R, Besser GM: Endocrine function, in Latner AL (ed): *Cantarow and Trumper Clinical Biochemistry*, ed 7. Philadelphia, WB Saunders Co, 1975, p 766.

Haemophilus influenzae Infections

Sir.—I recently cared for a previously healthy 13-month-old boy with meningitis due to *Haemophilus influenzae*. This was diagnosed by positive CSF and blood cultures obtained after 12 to 18 hours of persistent vomiting and progressively worsening lethargy.

Twenty-four hours after admission of this child, I was called to see his 3-year-old brother, who had begun vomiting six hours previously. Though his physical findings were entirely within normal limits, his temperature was 39.1 °C; WBC count, 10,800/cu mm, with a marked left shift to the left. Chest roentgenogram showed a definite alveolar infiltrate in the right upper lobe.

Blood and throat cultures yielded *H influenzae* sensitive to ampicillin. Intramuscular administration of ampicillin in a dose of 200 mg/kg brought about resolution of this child's fever within 24 hours. The brother with meningitis was fever free within 48 hours after treatment with ampicillin, 400 mg/kg intravenously, was begun. His culture had previously shown identical sensitivity patterns, prompting the discontinuation of chloramphenicol after 24 hours of combined ampicillin-chloramphenicol therapy.

In their article published in the July 1977 issue of the JOURNAL (131:778-781, 1977), Tejani et al, in their concluding statement, suggest that "protecting the infant in close contact with an index case of *H influenzae* disease may not be an unreasonable solution [to the eradication of the carrier state of *H influenzae*]."

Might not such therapy prevent early detection and proper culture identification in a child who already has *H influenzae* lurking in his bloodstream, ready to set up housekeeping in his lungs or spinal fluid? I suggest that careful observation and early, full-dose antibiotic therapy is more in line with my readings and training in infectious disease. Incidentally, both boys have been seen two weeks after their hospitalization; neither have suffered any sequelae from their illnesses.

I would appreciate comments and recommendations for following up approximately 20 children under age 5 exposed to these brothers at a day care facility.

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In Reply.—Dr Sawyer's second patient falls in the category that we prefer to call coprimary rather than secondary. In our review of intrafamily spread of *Haemophilus influenzae* infection in confirmed cases, the time interval between the disease in the index case and siblings ranged from 24 hours to two months, with a mean time interval being 8.5 days. Our present policy is to diagnose *H influenzae* meningitis expediently by smear (80% to 85% positive) and counterimmunoelectrophoresis (90% to 95% positive). Once a diagnosis is made, we ask the parents to bring in the siblings. Cultures are taken from all siblings, and those under 3 years of age are given ampicillin, 100 mg/kg/day orally, for ten days. Using this regimen, we have not seen a secondary or coprimary case in

two years. Siblings over 3 years of age, if culture positive, are also treated; the rationale here is to reduce interpersonal transmission of the organism rather than disinfect those already exposed.[1]

Our regimen, while preventing secondary cases, may not protect some cases of coprimary disease. The incidence of coprimary cases is about 25% to 30% of all intrafamily spread; thus, we would certainly avoid the large majority of intrafamily cases.

I am not convinced that we would "mask" the infection in the coprimary cases by starting prophylaxis. There are no data available regarding the culture recovery in prophylactically treated children, but a recent study shows a recovery rate of 13 of 14 cases where partially treated *H influenzae* meningitis is concerned.[2] Wehrle[3] concludes that the application of antimicrobial drugs in common use for treatment of ototis media does little to suppress *H influenzae* infection in the central nervous system. There should also be no difficulty in making a diagnosis of meningitis by inference in a "masked" case with equivocal signs when an index case has already been diagnosed in the same family.

Reasonable advice regarding the ever increasing problem of day care center prophylaxis is not yet clear, but recent evidence suggests that when two cases of *H influenzae* disease occur in a day care nursery, as in Dr Sawyer's area, prophylactic measures may be necessary. Ginsburg et al[4] discovered seven cases in a day care nursery over a 14-month period after an index case had appeared.

On the basis of presently available data, (1) all intimate contacts of the two brothers, including adults, should have cultures, and those who are culture positive should be treated with ampicillin since the organism was sensitive to ampicillin; (2) family members of infants who are positive for *H influenzae* type b should also be cultured and treated if they harbor the *H influenzae* type b; (3) the culture-positive children should be excluded from the nursery and not readmitted unless two successive negative cultures are obtained; and (4) if ampicillin is not successful in eradicating the carrier state, closing the facility temporarily or using trimethoprim-sulfamethoxazole or rifampin should be considered. Enough experience has not been accumulated to judge the toxicity of these two drugs in small children, but efficacy without side effects has been observed in two studies.[5,6]

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1. Finley RA: Prophylaxis against meningococcal disease. *JAMA* 236:459-461, 1976.
2. Converse GM, Gwaltney JM, Strassburg DA, et al: Alterations of cerebral spinal fluid findings by partial treatment of bacterial meningitis. *J Pediatr* 83:220-225, 1973.
3. Wehrle PF: Return of the lumbar tapper's dilemma. *J Pediatr* 83:351-352, 1973.
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6. Gilsdorf J, Granoff D, Gessert C, et al: *Hemophilus influenzae* type b infection in a day care center: Eradication of carrier state by rifampin. *Pediatr Res* 12:491, 1978.

Influenza Virus A_2 Infections

Sir.—We were interested to read the report by J. W. Paisley and colleagues in the JOURNAL (132:34, 1978) describing the clinical manifestations of influenza virus A_2 infections in young children. This article confirms several of the findings in our own published report of a similar group of children in hospital.[1] The main findings of both studies are compared in the accompanying Table.

In our study, gastrointestinal symptoms were the usual presentation in babies aged younger than 6 months of age. Fifty percent of the babies in this age group, nine of 18, had diarrhea and vomiting or diarrhea. Two babies required intravenous fluids and one had severe hypernatremic dehydration. Thus, of the 17 children who had diarrhea and vomiting or diarrhea alone, only four were older than 6 months of age.

The higher incidence of convulsions in our series, 37%, is mainly due to the higher incidence of febrile convulsions in the susceptible age group (24 of 35 children aged 1 to 3 years). This finding is similar to that of Brocklebank et al.[2]

The one child who died in our series[1] had congenital hydrocephalus and at postmortem showed histological signs of influenzal virus pneumonia and virus was cultured antemortem from brain biopsy specimen and postmortem from lung tissue. This was considered to support the diagnosis of viral encephalitis and pneumonitis.

Clearly, the manifestations of influenza virus A_2 infections are profoundly modified by the age of the host and epidemiological studies[3] must be critically reviewed if such considerations are ignored. Finally, the increased severity and mortality of this infection in children with major congenital defects may influence our views in prophylactic vaccination.

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1. Price DA, Postlethwaite RJ, Longson M: Influenza virus A_2 infections presenting with febrile convulsions and gastrointestinal symptoms in young children. *Clin Paediatr* 15:361-367, 1976.
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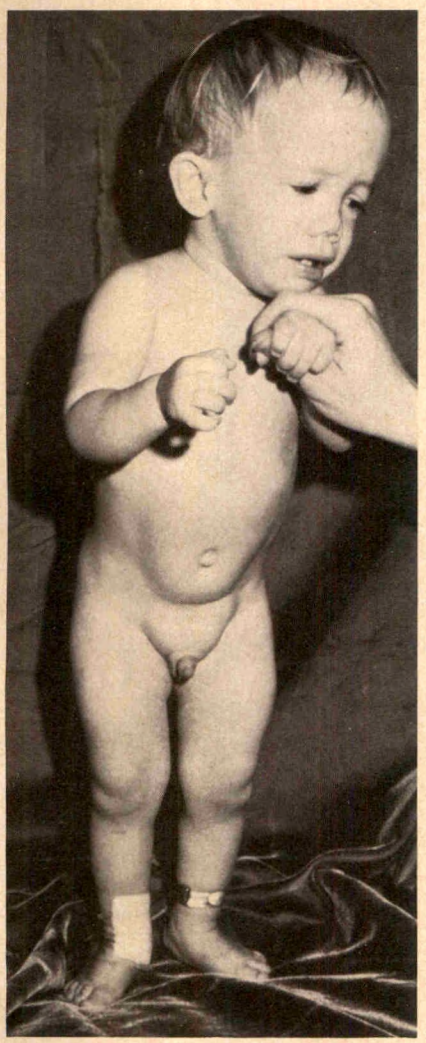
Clinical Features in Both Studies*

Clinical Features	Study by Paisley et al (N = 83)	Study by Price et al (N = 75)
Fever	91	87
Diarrhea or vomiting	49	53
Pharyngitis	34	72
Lower respiratory tract signs	29	32
Otitis media	24	44
Stridor	13	9
Conjunctivitis	13	1
Convulsions	19	37
Mortality	3.6%	1.3%

*Percentage of total number of children.

Microphallus, Growth Hormone Deficiency, and Hypoglycemia in Russell-Silver Syndrome

Sir.—We read with interest the letter of Sujansky and Riccardi (132:214, 1978) in response to the article by Marks and Bergeson (131:447-451, 1977) on the genital anomalies seen in Russell-Silver syndrome since we have followed up a very similar child for the last four years. The child was initially diagnosed as having Russell-Silver syndrome without asymmetry because of intrauterine growth retardation (birth weight at 36 weeks' gestation, 1,049 g; birth length, 36 cm), clinodactyly, partial soft-tissue syndactyly, microphallus (at 17 months of age, his penis measured 1.1 cm; no hypospadias was present), cryptorchidism, and a few episodes of poorly recorded hypoglycemia (Figure). However, at age 2 years and 9 months, endocrine evaluation disclosed that he had severe hypoglycemia with seizures, hypopituitarism including growth hormone deficiency, hypothyroidism, hypoadrenalism, and apparent hypogonadotropism (serum luteinizing hormone level, under 5 ImU/ml; follicle-stimulating hormone level, 6 ImU/ml).



Patient at 2 years of age. Note microphallus.

As with the syndrome of microphallus, growth hormone deficiency, and hypoglycemia described by Lovinger et al,[1] he has reponded to growth hormone therapy with catch-up growth and marked improvement of the episodes of hypoglycemia. He is presently growing parallel to, but just below, the third percentile, with a delayed bone age as would be typical for a Russell-Silver syndrome patient. Interestingly, on recent cystoscopy, at the time of repair of his cryptorchidism, it was noted that the verumontanum had a relatively large fossa, thought to be compatible with a vaginal remnant.

We thought that he was different from the patients described by Lovinger et al[1] because of his history of intrauterine growth retardation and he was different from the usual Russell-Silver dwarf because of his hypopituitarism. However, he bears some resemblance to the patient described by Sujansky and Riccardi, and we suspect that treating our patient with growth hormone has prevented the episodes of hypoglycemia leading to permanent CNS damage.

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Seattle, WA 98105

The National Institute of Arthritis, Metabolism, and Digestive Diseases and the National Pituitary Agency of the University of Maryland provided the growth hormone for our patient.

1. Lovinger RD, Kaplan SL, Grumbach MM: Congenital hypopituitarism associated with neonatal hypoglycemia and microphallus: Four cases secondary to hypothalamic hormone deficiencies. *J Pediatr* 87:1171-1181, 1975.

New Findings on Food Additives and Hyperkinesis

Sir.—This letter is an addendum to the MARGINAL COMMENT I prepared on food additives and hyperkinesis for the November issue of the JOURNAL (131:1204-1206, 1977). Some new findings make it necessary to modify slightly statements made there.

The study done by Goyette et al,[1] demonstrated no differences, using global behavioral measures, between children who received food colorings and those who did not under double-blind conditions. However, slight decreases in performance (not achieving statistical significance) were noted on a test of sustained attention only when the test was administered in the first two hours after ingestion of food colorings. I commented that this finding needed replication.

Connors has completed a study designed to test this finding using behavioral measures rather than the test of sustained attention.[1] Parents of 13 preschool, hyperkinetic children were asked to rate behavior, confining their observations to a three-hour period immediately following the ingestion of food colorings or a placebo. Under these conditions, behavior worsened when the subjects consumed food coloring as compared with the controls ($P < .025$).

It does seem that some kind of behavioral difference can be seen for a short period of time after the ingestion of food colorings in preschool children. However, there does not seem to be any relationship between that finding and more global measures of behavior at home and school during the day, which suggests that the behavioral change is subtle and of questionable clinical significance. These findings suggest many new questions that need to be studied. For example, is this brief change in behavior related to the dose of food colorings? Are the findings in preschool children different from those in older children? Would it make a difference in the global ratings if food colorings were ingested more frequently, eg, every hour or two?

While these questions await answers, I remain impressed that global changes in behavior can be detected easily in open clinical trials but disappear strikingly under controlled, double-blind conditions. These new findings do not support the Feingold hypothesis, but they do make the issue more complicated and should stimulate more careful research.

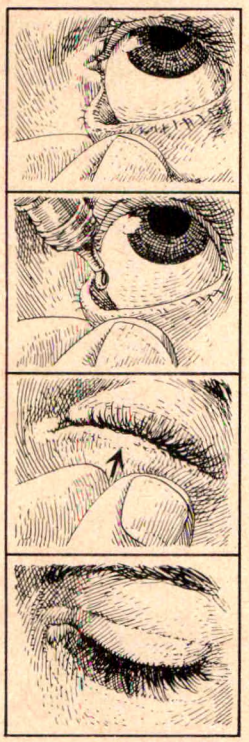
ESTHER H. WENDER, MD
The University of Utah
Salt Lake City, Utah

1. Goyette CH, Connors CK, Petti TA, et al: Effects of artificial colors on hyperkinetic children: A double-blind challenge study. *Psychopharmacol Bull* 14:39, 1978.

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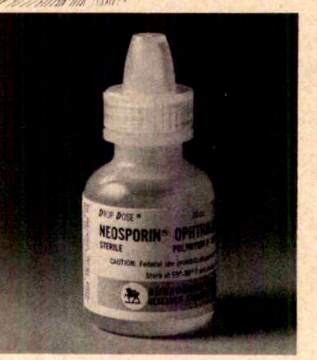


1
Have patient put head back. Gently pull lower eyelid away from eye to make a pouch. Have the patient look up.

2
Put one drop into the cul-de-sac (conjunctival pouch) without touching the eyelid or lashes.

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4
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1. Fraunfelder FT, Hurwitz J, Marsey M: Presentation at Las Vegas Meeting of Association for Research in Vision and Ophthalmology and the American Academy of Ophthalmology and Otolaryngology, Oct 6, 1976, as reported in *Clinical Trends in Ophthalmology*, April 1977.

In a controlled study comparing a variety of common techniques, retention of eye drops on the eye after a five-minute interval went from 16% to 53% when the pouch technique was utilized in the under 20 age group. A 64% retention rate was achieved in the 50–60-year-old age group.

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While every precaution is taken to insure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.

Books

Fragile Families, Troubled Children: The Aftermath of Infant Trauma, by Elizabeth Elmer, $7.95, 160 pp, Pittsburgh, University of Pittsburgh Press, 1978.

This book reports an eight-year follow-up study of abused infants first seen when they were younger than 1 year of age. A one-year follow-up was published in 1967.[1] The present publication compares the outcome in 17 abused children with an equal number of children matched for age, race, sex, and socioeconomic status initially seen because of an accident and with a matched group without a history of abuse or accident. The social class of these children was predominantly low.

The initial hypotheses were that the abused children would achieve less than the other groups in health, physical development, intellectual functioning, language, and self-concept, and would rate higher in impulsivity and aggression. In actuality, eight years later, few differences could be documented. All groups were replete with a variety of health, speech, school, and emotional difficulties.

That children, younger than 1 year of age, in the study identified as abused have about the same outcome eight years later as their peers from the same lower socioeconomic group raises a question about the use of child abuse as an intervention alert. So many other children, even though not abused, are obviously at equal developmental risk. Although the data are of great interest, their implications would have been strengthened if several child health indices had been simultaneously determined in a defined child health population in the community. Such a study would delineate not only the problems of children in such a population, but also actual or potential strengths and resources which might be mobilized in the service of child health.

A number of recent publications support the findings of this study as to the overwhelming importance of social, economic, and family forces on both children and their parents.[2-4] What seems needed is a blending of the traditional clinical approach to individual children around individual encounters in health or illness and a community approach that encompasses the needs of all children in that population.

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1. Elmer E: *Children in Jeopardy.* Pittsburgh, University of Pittsburgh Press, 1967.
2. Keniston K, Carnegie Council on Children: *All Our Children: The American Family Under Pressure.* New York, Harcourt Brace Jovanovich, 1977.
3. Miller FJW, Court SDM, Knox EG, et al: *The School Years in Newcastle upon Tyne.* London, Oxford University Press, 1974.
4. Committee on Child Health Services: *Fit for the Future.* London, Her Majesty's Stationery Office, vol 1, December 1976.

Clinical Pediatric Oncology, ed 2, edited by Wataru W. Sutow, Teresa J. Vietti, and Donald J. Fernbach, 751 pp, $44.50, CV Mosby Co, 1977.

The second edition of *Clinical Pediatric Oncology* is an excellent revision of an already classic text. It divides naturally into two related parts, basic concepts of care of the child with cancer and discussion of specific cancers. The material discussing basic concepts now occupies more than 40% of the text. Many of these chapters have been revised from the first edition. Chapters on genetic considerations, immunology and immunotherapy, newer techniques in diagnostic radiology, and rehabilitation have been added. The chapter on genetics of childhood cancer is timely and well done. The concept of rehabilitation is becoming more firmly entrenched as the number of long-term survivors increases. These chapters have been nicely integrated with revised and updated chapters on the basic concepts of cancer management. Indeed, the chapters on chemotherapy provide excellent background in pharmacokinetics and the practical aspects of drug therapy. Though these first chapters have several authors, they flow from one to another very smoothly.

At least one chapter is devoted to each of the major sites of cancer. They provide reviews of the epidemiology, natural history, pathology, and treatment for each site. Though occasionally limited in depth, each chapter does provide an overview of that cancer. The majority of the data presented is from the Southwest Oncology Group and the M.D. Anderson Hospital and Tumor Institute, but other sources are used when appropriate. Within the limits of any textbook, the therapies recommended are current. Each chapter is well referenced and we commend the selected readings lists provided for most chapters.

This textbook remains the predominant single source for information on childhood cancer. Its tone reflects the positive attitude surrounding the management of childhood cancer. The emphasis on basic concepts and comprehensive care seem nicely balanced. We believe the text will be a valuable resource for all professionals dealing with a child who has cancer. It provides an educational tool and a source for details necessary in the evaluation of a child suspected of having cancer.

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Heart Disease in Infants, Children and Adolescents, ed 2, edited by Arthur J. Moss, Forrest H. Adams, and George C. Emmanouilides, 757 pp, with illus, Baltimore, Williams & Wilkins Co, 1977.

The editors of this book have selected 74 contributors from 33 centers to encompass the topics in pediatric cardiology. Each chapter includes an extensive selection of references.

The first chapter, written by James Nora, is concerned with the etiologic aspects of congenital heart disease. His tables of autosomal dominant, recessive, and sex-linked syndromes will be helpful in investigating causes of heart disease when associated with other malformations. Forrest Adams describes fetal circulation and the alterations that occur after birth. Jerome Liebman and Robert Plonsey present electrocardiography along with tables of normal values for heart rate, PR interval, and amplitude of R and S waves in the precordial leads. Criteria for ventricular hypertrophy are designated. The intricacies of vectorcardiography are related by Samuel Sapin, with illustrations and tables of normal values for age.

Richard Meyer, a pioneer in the field of pediatric echocardiography, amply covers the subject and provides superb echocardiograms of many forms of congenital heart disease. These recordings and the discussion are ideal to aid the novice in identification of cardiac anomalies from echocardiograms. Methods for assessing ventricular performance from echocardiograms are included. Jay Jarmakani wrote the section on cardiac catheterization. He covers the field from types of catheters to equations for calculation of vascular resistance and valve areas.

The second section of this book is devoted to congenital cardiac defects. Robert Feldt and William Weidman discuss defects of the atrial septum and endocardial cushion. They include idealized diagrams, angiograms, and echocardiograms. Aspects of differential diagnosis, treatment, and surgical management of defects of the ventricular septum are elucidated by Graham, Bender, and Spach. Riemenschneider and Moss review the problems of left ventricular-right atrial communications. Michael Heymann expands on the pathophysiology of patent ductus arteriosus in newborns and older children. Friedman and Kirkpatrick review the types of aortic stenosis, including obstructive asymmetric septal hypertrophy and techniques for the differentiation. Hartmann et al portray coarctation of the aorta with angiographic illustrations. Sissman describes anomalies of the aortic arch with schematic diagrams of their embryologic origins. Obstructive lesions of the right ventricle and pulmonary arterial tree, along with congenital absence of the pulmonary valve, are portrayed by Emmanouilides. Anomalies of the tricuspid valve are described by Van Mierop, Schiebler, and Victorica. The many facets of the tetrad of Fallot are brought out by Guntheroth and Kawabori. Tricuspid atresia is dealt with by Amnon Rosenthal. An excellent presentation of D-transposition of the great arteries is provided by Milton Paul. He describes techniques of balloon atrial septostomy and provides illustrations along with a summary of the results. He also reviews the complications of surgical redirection of blood flow by the atrial baffle approach. Ruttenberg portrays the anatomy of corrected transposition of the great arteries. The anatomic orientation of double outlet right ventricle is reviewed by Neufeld and Randall. Van Praagh and Weinberg explain double-outlet left ventricle. Van Praagh includes a classification of anatomic types, photographs of specimens, and angiocardiograms. Schematic drawings by Elliot, Bream, and Gessner help in comprehension of the relations of single and common ventricle. The Van Praaghs and Weinberg tackle the subject of malposition of the heart. Cardiac loop formation and types of conus are illustrated. I recommend this section for the novice and the cardiologist. Mair and Ritter illustrate the repair of truncus arteriosus and list the associated anomalies. Noonan reviews hypoplastic left heart syndrome. Anomalous venous connections are illustrated by Lucas and Schmidt. Idealized diagrams aid in understanding the variants of cor triatriatum. A review of cases of arteriovenous fistulas are presented by Jimenez, Guillen and Gussoni. Paul Lurie discusses abnormalities and diseases of coronary vessels. The disorder of endocardial fibroelastosis is reviewed by Hastreiter and Fisher and diseases of the mitral valve by Steinfeld.

A succinct review of acute rheumatic fever was written by Lewis Wannamaker and Edward Kaplan. Chronic rheumatic heart disease is encompassed by Samuel Kaplan. Its impact in developing countries are related by Aryanpur, Nazarian, and Siassi. Manifestations of infective carditis are related by Blumenthal. Nonrheumatic inflammatory cardiovascular diseases are dealt with by Noren, Kaplan, and Staley.

Although pediatric cardiologists spend little time with metabolic and nutritional disease of the heart, Whittemore and Caddell thoroughly explore this field. Perhaps the section on the presentation of the various types of glycogen storage disease could have been expanded to aid the cardiologist in its recognition. The clinical features of mucopolysaccharidoses, Friedreich's ataxia, progressive muscular dystrophy, juvenile rheumatoid arthritis, Marfan's syndrome, and amyloidosis are the subject of a chapter by Anderson and Moller.

The last section of the book covers heart disease in the newborn (Lees and Sunderland), pulmonary hypertension (Vogel), systemic hypertension (Loggie), heart failure (Talner), arrhythmias (Roberts and Gelband), cardiac tumors (Edwards), postoperative syndromes (Engle), atherosclerosis (Carter and Lauer), and the adolescent (Neill and Haroutunian).

In reviewing this book, I chose to refer to practically all of its chapters in order to give the reader an idea of breadth of its content and the selection of its authors.

The positive features of this book include an up-to-date presentation of most topics by experts, the inclusion of echocardiographic characteristics of cardiac anomalies, the extensive number of topics covered, the plethora of references, and the superb illustrations.

The section on congestive cardiac failure does not include vasodilating agents, which may not have been in significant use when this section was written. Perhaps the book should include a more extensive section on pacemaker implantation and modes of follow-up.

I highly recommend the book to anyne who desires a treatise on pediatric cardiology.

G. BENZING III, MD
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Books Received But Not Reviewed

Decision Making and the Defective Newborn, by Chester A. Swinyard, $24.75, 649 pp, Springfield, Ill, Charles C. Thomas Publishing Co, 1977.

L'Enfant Infirme Moteur D'Orgine Cerebrale, by M. Cahuzac, 474 pp, Paris, Masson Publishers, 1977.

Entretiens de Chirurgie Infantile, edited by Hopital Trousseau, 190 pp, Paris, Expansion Scientifique, 1977.

Antimicrobial Chemotherapy for Newborns, by Nelson McCracken, $16.50, 177 pp, New York, Grune & Stratton Inc, 1977.

The Infant Center: A Complete Guide to Organizing and Managing Infant Day Care, by Emily Herbert-Jackson, Marion O'Brien, Jan Porterfield, and Todd R. Risley, $15.75, 244 pp, Baltimore, University Park Press, 1977.

Toxicologic Emergencies: A Handbook in Problem Solving, by Lewis R. Goldfrank and Robert Kirstein, $9.75, 180 pp, New York, Appleton-Century-Crofts, 1977.

Taxonomy of Behaviour Disturbance, by D.H. Stott, N. C. Marston, and S. J. Neill, $9.50, 184 pp, London, University of London Press Ltd, 1975.

Developmental Paediatrics (Postgraduate Paediatrics Series), edited by John Apley and K. S. Holt, $11.95, 311 pp, Boston, Butterworth's Publishing Co, 1977.

Annual Progress in Child Psychiatry and Child Development 1977, ed 10, edited by Stella Chess and Alexander Thomas, $20, 782 pp, New York, Brunner/Mazel Inc, 1977.

Child Care in General Practice, edited by Cyril Hart, $16, 442 pp, New York, Churchill Livingstone, 1977.



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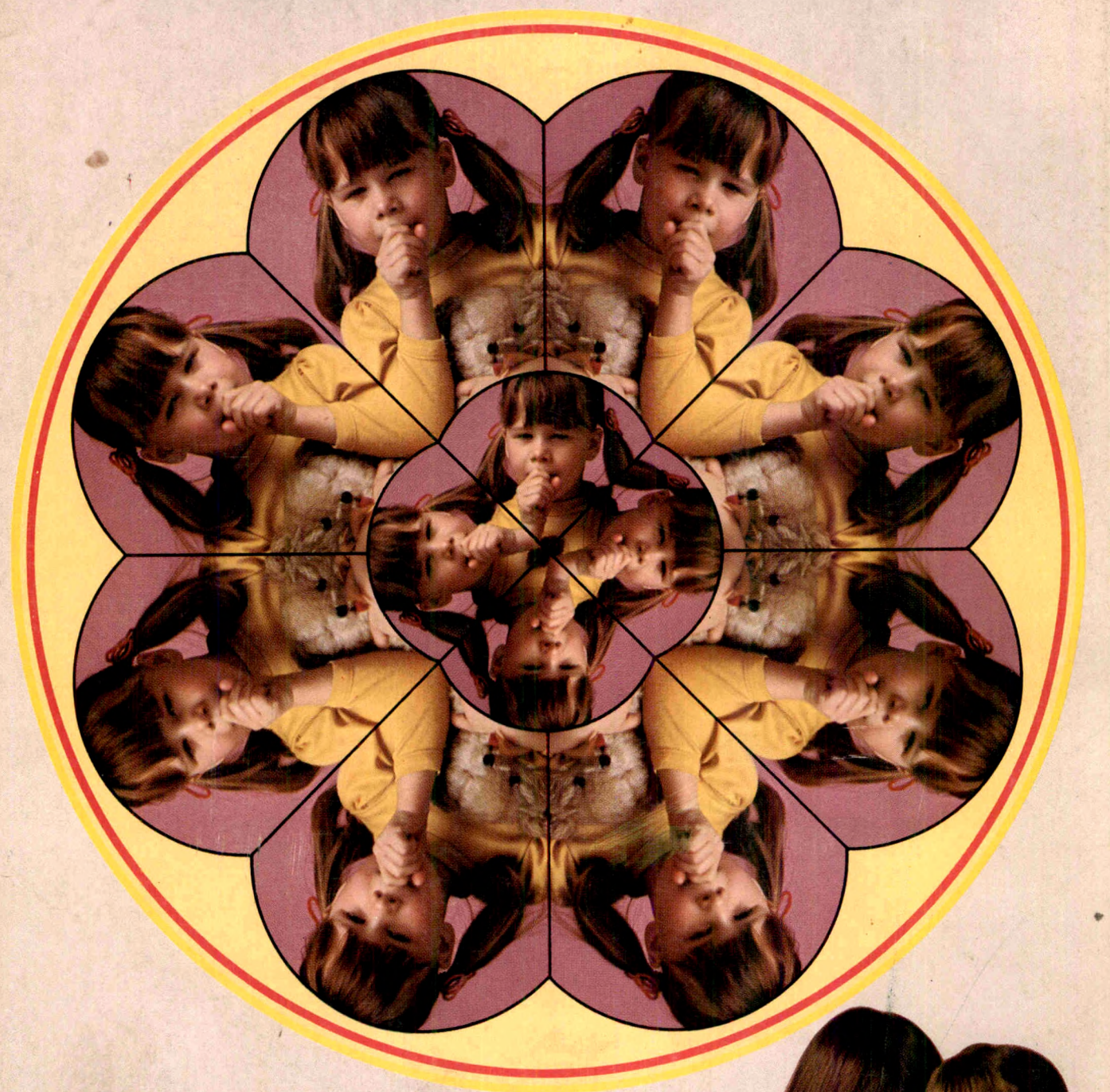
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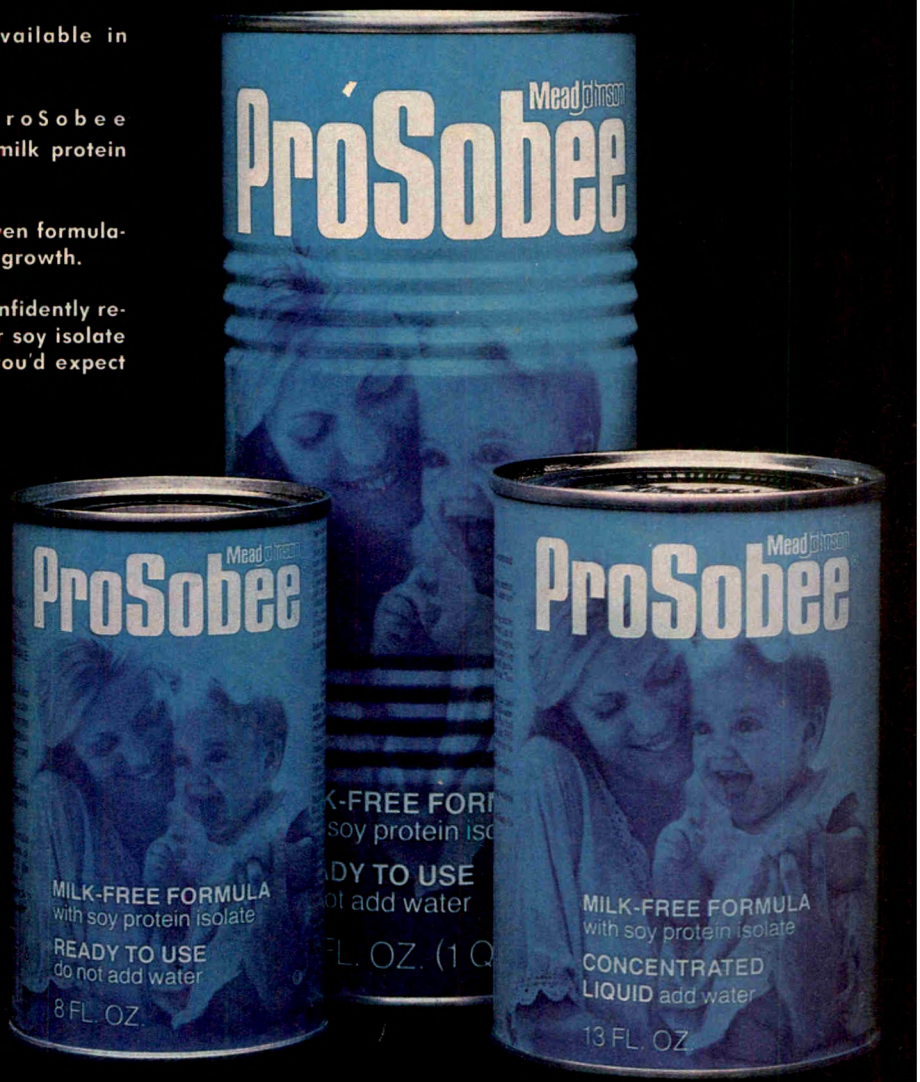
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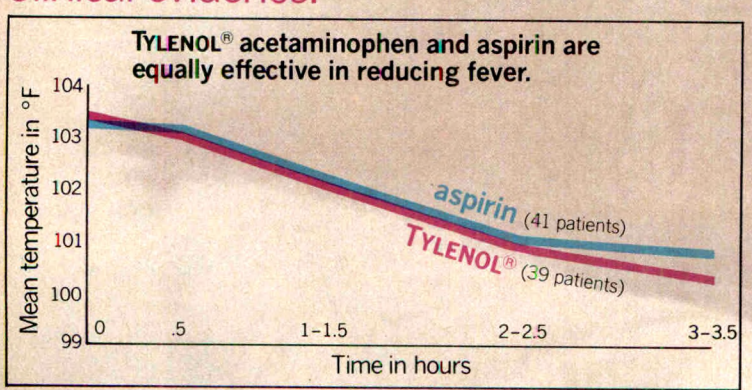
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In each study, Ilosone was shown to be effective at a dosage of 20 mg/kg/day.*

*Data on file, Dista Products Company.

Hepatic dysfunction with or without jaundice has occurred, chiefly in adults, in association with erythromycin estolate administration.

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Ilosone® (erythromycin estolate)

Brief Summary.
Consult the package literature for prescribing information.

WARNING

Hepatic dysfunction with or without jaundice has occurred, chiefly in adults, in association with erythromycin estolate administration. It may be accompanied by malaise, nausea, vomiting, abdominal colic, and fever. In some instances, severe abdominal pain may simulate an abdominal surgical emergency.

If the above findings occur, discontinue Ilosone promptly.

Ilosone is contraindicated for patients with a known history of sensitivity to this drug and for those with preexisting liver disease.

Indications: Included among the indications for this drug is *Streptococcus pyogenes* (Group A Beta-Hemolytic)—Upper and lower respiratory tract, skin, and soft-tissue infections of mild to moderate severity.

Injectable penicillin G benzathine is considered by the American Heart Association to be the drug of choice in the treatment and prevention of streptococcal pharyngitis and in long-term prophylaxis of rheumatic fever.

When oral medication is preferred for treating the above-mentioned conditions, penicillin G or V or erythromycin is the alternate drug of choice.

The importance of the patient's strict adherence to the prescribed dosage regimen must be stressed when oral medication is given. A therapeutic dose should be administered for at least ten days.

Consult the package literature for other indications.

Contraindication: Known hypersensitivity to this antibiotic.

Warnings: (*See* Warning box above.) The administration of erythromycin estolate has been associated with the infrequent occurrence of cholestatic hepatitis. Laboratory findings have been characterized by abnormal hepatic function test values, peripheral eosinophilia, and leukocytosis. Symptoms may include malaise, nausea, vomiting, abdominal cramps, and fever. Jaundice may or may not be present. In some instances, severe abdominal pain may simulate the pain of biliary colic, pancreatitis, perforated ulcer, or an acute abdominal surgical problem. In other instances, clinical symptoms and results of liver function tests have resembled findings in extrahepatic obstructive jaundice.

Initial symptoms have developed in some cases after a few days of treatment but generally have followed one or two weeks of continuous therapy. Symptoms reappear promptly, usually within 48 hours after the drug is readministered to sensitive patients. The syndrome seems to result from a form of sensitization, occurs chiefly in adults, and has been reversible when medication is discontinued.

Usage in Pregnancy—Safety of this drug for use during pregnancy has not been established.

Precautions: Caution should be exercised in administering the antibiotic to patients with impaired hepatic function.

Surgical procedures should be performed when indicated.

Adverse Reactions: The most frequent side effects are gastrointestinal (e.g., abdominal cramping and discomfort) and are dose related. Nausea, vomiting, and diarrhea occur infrequently with usual oral doses.

During prolonged or repeated therapy, there is a possibility of overgrowth of nonsusceptible bacteria or fungi. If such infections arise, the drug should be discontinued and appropriate therapy instituted.

Mild allergic reactions, such as urticaria and other skin rashes, have occurred. Serious allergic reactions, including anaphylaxis, have been reported.

Administration and Dosage: *Adults*—The usual dosage is 250 mg every six hours. This may be increased up to 4 gm or more per day according to the severity of the infection.

Children—Age, weight, and severity of the infection are important factors in determining the proper dosage. The usual regimen is 30 to 50 mg per kg per day in divided doses. For more severe infections, this dosage may be doubled.

If administration is desired on a twice-a-day schedule in either adults or children, one-half of the total daily dose may be given every 12 hours.

Streptococcal Infections—For the treatment of streptococcal pharyngitis and tonsillitis, the usual dosage range is 20 to 50 mg per kg per day in divided doses.

Body Weight	Total Daily Dose
10 kg or less (less than 25 lb)	250 mg
11-18 kg (25-40 lb)	375 mg
18-25 kg (40-55 lb)	500 mg
25-36 kg (55-80 lb)	750 mg
36 kg or more (more than 80 lb)	1000 mg (adult dose)

In the treatment of group A beta-hemolytic streptococcal infections, a therapeutic dosage of erythromycin should be administered for at least ten days. In continuous prophylaxis of streptococcal infections in persons with a history of rheumatic heart disease, the dosage is 250 mg twice a day.

Consult the package literature for further dosage information.

[060278]

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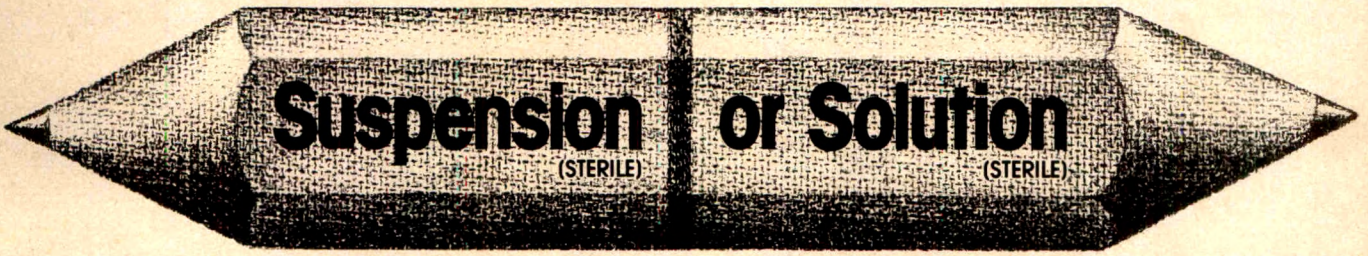
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(polymyxin B-neomycin-hydrocortisone)



INDICATIONS:
For the treatment of superficial bacterial infections of the external auditory canal caused by organisms susceptible to the action of the antibiotics, and for the treatment of infections of mastoidectomy and fenestration cavities caused by organisms susceptible to the antibiotics.

DESCRIPTION:
Each cc contains: Aerosporin® brand
Polymyxin B Sulfate ..... 10,000 units
Neomycin Sulfate ..... 5 mg
(equivalent to 3.5 mg neomycin base)
Hydrocortisone ..... 10 mg (1%)
The vehicle contains the inactive ingredients cetyl alcohol, propylene glycol, polysorbate 80, purified water and thimerosal (preservative) 0.01%.

PRECAUTIONS:
This drug should be used with care in cases of perforated eardrum and in long-standing cases of chronic otitis media because of the possibility of ototoxicity caused by neomycin.

ADVERSE REACTIONS:
Neomycin is a not uncommon cutaneous sensitizer. There are articles in the current literature that indicate an increase in the prevalence of persons sensitive to neomycin.

BENEFITS:
Indications include infections of mastoidectomy and fenestration cavities caused by organisms susceptible to the antibiotics.

INDICATIONS:
For the treatment of superficial bacterial infections of the external auditory canal caused by organisms susceptible to the action of the antibiotics.

DESCRIPTION:
Each cc contains: Aerosporin® brand
Polymyxin B Sulfate ..... 10,000 units
Neomycin Sulfate ..... 5 mg
(equivalent to 3.5 mg neomycin base)
Hydrocortisone ..... 10 mg (1%)
The vehicle contains the inactive ingredients glycerin, hydrochloric acid, propylene glycol, purified water and potassium metabisulfite (preservative) 0.1%.

PRECAUTIONS:
This drug should be used with care when the integrity of the tympanic membrane is in question because of the possibility of ototoxicity caused by neomycin.

ADVERSE REACTIONS:
Neomycin is a not uncommon cutaneous sensitizer. There are articles in the current literature that indicate an increase in the prevalence of persons sensitive to neomycin. Stinging and burning have been reported when this drug has gained access to the middle ear.

BENEFITS:
Clear visualization of field. Does not have to be shaken.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS COMMON TO BOTH PRODUCTS:

CONTRAINDICATIONS:
In individuals who have shown hypersensitivity to any of the components, and in herpes simplex, vaccinia, and varicella.

WARNINGS:
Prolonged treatment may result in overgrowth of non-susceptible organisms and fungi. If the infection is not improved after one week, cultures and susceptibility tests should be repeated to verify the identity of the organism, and to determine whether therapy should be changed.

When using neomycin-containing products to control secondary infection in the chronic dermatoses, such as otitis externa, it should be borne in mind that the skin in these conditions is more liable than is normal skin to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling, and itching; it may be manifest simply as a failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

PRECAUTIONS:
If sensitization or irritation occurs, medication should be discontinued promptly. Patients who prefer to warm the medication before using should be cautioned against heating the solution above body temperature, in order to avoid loss of potency.

Treatment should not be continued for longer than ten days. Allergic cross-reactions may occur which could prevent the use of any or all of the following antibiotics for the treatment of future infections: kanamycin, paromomycin, streptomycin, and possibly gentamicin.

HOW SUPPLIED:
Both products available in 10 cc bottles with sterile droppers.

Both products offer you:

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Each capsule or tablespoon (15 ml) elixir contains theophylline (anhydrous) 150 mg and glyceryl guaiacolate (guaifenesin) 90 mg. Elixir: alcohol 15%

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Indications: For the symptomatic relief of bronchospastic conditions such as bronchial asthma, chronic bronchitis, and pulmonary emphysema.

Warnings: Do not administer more frequently than every 6 hours, or within 12 hours after rectal dose of any preparation containing theophylline or aminophylline. Do not give other compounds containing xanthine derivatives concurrently.

Precautions: Use with caution in patients with cardiac disease, hepatic or renal impairment. Concurrent administration with certain antibiotics, i.e. clindamycin, erythromycin, troleandomycin, may result in higher serum levels of theophylline. Plasma prothrombin and factor V may increase, but any clinical effect is likely to be small. Metabolites of guaifenesin may contribute to increased urinary 5-hydroxyindoleacetic acid readings, when determined with nitrosonaphtol reagent. Safe use in pregnancy has not been established. Use in case of pregnancy only when clearly needed.

Adverse Reactions: Theophylline may exert some stimulating effect on the central nervous system. Its administration may cause local irritation of the gastric mucosa, with possible gastric discomfort, nausea, and vomiting. The frequency of adverse reactions is related to the serum theophylline level and is not usually a problem at serum theophylline levels below 20 μg/ml.

How Supplied: Capsules in bottles of 100 and 1000 and unit-dose packs of 100; Elixir in bottles of 1 pint and 1 gallon.

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PHARMACEUTICAL DIVISION

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Necrotizing Enterocolitis

Although the pathogenesis of necrotizing enterocolitis (NEC) has yet to be delineated, there is ample evidence to support a role of intestinal bacteria in the genesis and complications of this disease in neonates. The importance of coliform bacilli has been demonstrated in experimental NEC in newborn rats, and sporadic outbreaks of NEC in neonatal intensive care units have frequently been associated with intestinal colonization or septicemia caused by various members of the Enterobacteriaceae family.[1,2] Stanley and Null[3] reported that temporal alterations in the intestinal microflora of infants were correlated with changes in the incidence of NEC and that neonates initially colonized with *Klebsiella pneumoniae* had an almost threefold greater likelihood of developing disease than those colonized with other enterobacterial species. Surveillance studies from one intensive care unit have shown that *K pneumoniae* and *Escherichia coli* strains are recovered significantly ($P < .01$) more often from rectal cultures of infants with NEC than from their cohorts without NEC.[4] These data support the contention that the fecal microflora contribute in some way to the pathogenesis of necrotizing enterocolitis.

That orally administered aminoglycosides might be efficacious in management of patients with NEC was suggested by Bell and co-workers,[5] who reported a reduced incidence of intestinal perforation in affected infants treated orally with kanamycin sulfate or gentamicin sulfate. Egan and associates[6] and Boyle et al[7] demonstrated a reduced number of NEC cases in high-risk infants treated with kanamycin. However, a significant ($P = .038$) difference in incidence rates of NEC was only demonstrated in the Egan study. In addition, Rowley and Dahlenburg[8] have recently reported the results of a placebo-controlled trial in which gentamicin given orally did not provide protection from development of NEC. If an antimicrobial regimen is to be protective, it would presumably be on the basis of the substantial reduction in the number of Gram-negative enteric bacteria colonizing the bowel of orally treated infants.[7-9]

The report of a randomized double-blind controlled trial of oral gentamicin prophylaxis in infants considered at high-risk of developing NEC appears in this issue of the JOURNAL (p 1192). This regimen was successful in preventing NEC and NEC-like enteropathies. Grylack and Scanlon's enthusiasm for prophylaxis is reflected by their recommendation that gentamicin be given orally to all infants possibly at risk of developing NEC. *Is this recommendation justified?*

We believe that the aminoglycosides should not be used *routinely* for prevention of neonatal necrotizing enterocolitis, or, if used, prophylaxis should be restricted to a small number of high-risk infants and given only for a limited period of time. Our cautionary position is not because the data are unconvincing; rather, we are concerned that emergence of resistant strains will develop among previously susceptible enteric Gram-negative bacilli. This has certainly been the case with parenterally administered aminoglycosides in nurseries,[10,11] and one would predict that oral therapy will exert a more rapid selective pressure on the intestinal microflora. For example, in the study by Boyle and co-workers,[7] development of kanamycin resistance occurred in almost half of the infants receiving kanamycin orally, and the rate of colonization by resistant coliforms on days 17 through 30 of therapy was significantly ($P < .05$) greater in kanamycin-treated than in placebo-treated infants. In Gainesville, Fla, kanamycin was used routinely in all low-birth-weight infants after completion of the controlled prophylaxis trial in 1975.[6] Surveillance studies disclosed that a substantial percentage of *Staphylococcus epidermidis* and *S aureus* strains were resistant to kanamycin, gentamicin, and tobramycin. Additionally, approximately 10% of coliforms were resistant to these aminoglycosides.

Possible, untested, alternative candidates for oral prophylaxis are the polymyxins. These agents have bactericidal activity sharply limited to Gram-negative bacteria and have been used safely by the oral route for therapy of gastroenteritis caused by enteropathogenic *E coli*. Development of bacterial resistance to the polymyx-

ins is infrequent and, if encountered, would not jeopardize newborn care, since these drugs are rarely used for therapy of systemic bacterial diseases.

It should be pointed out that the oral administration of antimicrobials that selectively suppress the coliform flora of the gut will promote growth of other bacteria, some of which may be deleterious. It has recently been shown that antibiotic-associated pseudomembranous colitis is most likely caused by proliferation of toxin-producing clostridial strains that are resistant to the ingested drugs.[12,13] This entity has not been demonstrated in newborn infants, but *Clostridia* have been implicated in the etiology of NEC[14] or NEC-like illnesses,[15] and these organisms are resistant to the aminoglycosides and polymyxins.[16]

Because of the anticipated rapid emergence of resistant enteric bacteria and of the possible selective growth of potentially harmful members of the bowel microflora, we do not believe that either kanamycin or gentamicin should be used orally *routinely* for prevention of NEC. Although the number of infants receiving prophylaxis at any one time would be small, it is likely that they would constitute a substantial portion of the high-risk, low-birth-weight population in the unit, and this could have an important impact on the development of resistant organisms throughout the entire unit.

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Circumcision

Opponents of routine circumcision of the male infant will greet with pleasure the appearance of the article by Annunziato and Goldblum (p 1187) and the one by Sussman et al (p 1189) on unusual complications of the operation. Those who favor routine circumcision will be quick to point out that Fournier's syndrome and the scalded skin syndrome are very rare complications that should not deter parents from requesting circumcision for the newborn boy.

Circumcision of the newborn continues for the following reasons: it may be routine because of religious beliefs, and parents and physicians have for years accepted the procedure on the basis of arguments that the circumcised male is at less risk of having cancer of the penis develop, and that a malignant neoplasm in the genital tract of women married to circumcised men is less frequent than in women married to uncircumcised men. It is an incontestable fact at this point that there are more deaths each year from complications of circumcision than from cancer of the penis. In addition, there are no solid data to prove that the end of man's arrogance is related to the risk of malignancy in the female. Perhaps the only sound argument for routine circumcision of the male came from World War II, during which soldiers in the South

Pacific fought in swampy terrain in a hot, humid atmosphere and were unable to maintain even minimal hygiene. Under those conditions, the circumcised individual fared much better than the uncircumcised. In all likelihood, in a major war of the future, the great mushroom cloud will hardly distinguish between the circumcised and the uncircumcised.

It is unlikely that a listing of the hazards of circumcision will deter parents who insist on circumcision of their infant for religious reasons. However, for all other parents, physicians should become much more vociferous than they have been in discouraging circumcision of the newborn. They have been slow to do so because they themselves have not been convinced that circumcision is of little benefit. Yet, today, especially, the circumcised infant is at greater risk than ever before. He is clustered in large newborn nurseries (because small units are too costly) and is thereby exposed to even greater numbers of organisms that have been altered by their own exposure to multiple antibiotics. He has enough portals of entry for organisms as it is—his nose, mouth, conjunctivas, and the end of his umbilicus. It seems totally unnecessary to aid and abet lurking bacteria by adding a raw wound to his genitalia.

Finally, I should like to cast my vote against the use of the term Fournier's syndrome and beg that the condition be referred to as gangrene of penis, scrotum, or perineum. There are already far too many syndromes. The reader in two weeks or even less will be hard put to recall the meaning of the name, but he is unlikely to be confused by the term gangrene. Down, I say, with both circumcision and Fournier's syndrome.

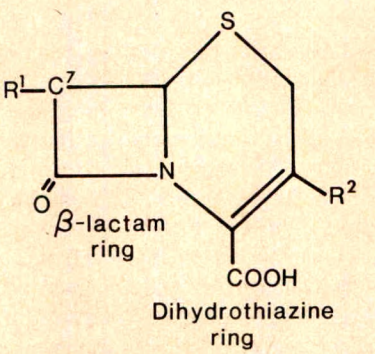
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The Cephalosporins

Are They as Important as Their Numbers Suggest?

Are you confused by the number of different cephalosporins that have been produced in recent years? I am. But the best (? worst) is still to come. There are approximately ten cephalosporins that are commercially available in the United States at the present time. At least an equal number of derivatives are under study, with several more on the horizon. Yet I cannot think of a pediatric infectious disease where cephalosporins deserve first consideration. Of course, they are frequently prescribed for patients allergic to penicillin, in the initial therapy of high-risk patients (usually combined with an aminoglycoside), and in the prevention of wound infections in contaminated surgical cases. Penicillin allergy and gastrointestinal surgery requiring antibacterial prophylaxis are much more common in adults. The use of cephalosporins alone for high-risk pediatric patients (eg, newborns, leukemia, burns, etc) is dangerous because of the prevalence of *Haemophilus* infections and the resistance of these bacteria, as well as *Enterobacter*, enterococcus, indole-positive *Proteus*, *Citrobacter*, *Providencia*, *Bacteroides*, *Neisseria*, and *Pseudomonas*, to many of the cephalosporins.

Where did it all start and where is it going? Professor Guisseppe Brotzu isolated a fungus, *Cephalosporium acremonium* from sea water near a sewage outlet off the coast of Sardinia in 1945.[1] He noted antibiotic activity among the metabolic products of this organism. Eight years later, one of these metabolic products, cephalosporin C, was discovered and, in 1962, cephalothin (the first clinically useful cephalosporin) was synthesized. Since then a series of chemical modifications in the 3 and 7 positions of the 7-aminocephalosporanic acid nucleus (Figure) have produced cephalosporins with varying degrees of protein binding, acid stability, resistance to β-lactamases, and in vivo distribution characteristics. I have listed some of these products in the accompanying table (not included are cephatrizine, cephacetile, cephaloglycin, cefazaflur, ceftezole, FR 10024, CGP 9000, and HR756). The importance of many of the pharmacologic differences among the cephalosporins is unclear (eg, protein binding and its relationship to distribution and activity[2]), yet the promise of increased activity against β-lactamase-positive and β-lactamase-



Chemical structure of cephalosporins.

Properties of Cephalosporins

Drug	Recommended Route of Administration	Protein Binding, (%)	Serum Half-life, hr	Advantages	Disadvantages
Cephalothin	Intravenous (IV)	70	0.5	Low toxicity	Desacetylated, painful intramuscularly
Cephaloridine	Intramuscular (IM),IV	20	1.1	Good tissue distribution, less pain intramuscularly	Hydrolyzed by some β-lactamases, nephrotoxic, probenecid ineffective
Cefazolin	IM,IV	80	1.5	High serum levels, less pain intramuscularly	Highly protein bound, hydrolyzed by some β-lactamases
Cephapirin	IM,IV	45	0.7	. . .	Desacetylated
Cefoxitin*	IM,IV	70	0.7	Active against *Bacteroides*	Phlebitis
Cefuroxime	IM,IV	33	1.1	Active against *Citrobacter* and *Enterobacter*	. . .
Cefamandole	IM,IV	74	0.6	Active vs *Haemophilus, Neisseria, Enterobacter*	Separate disc test required
SKF 75073	IM,IV	98	1.5†	Active against *H influenzae*	Human data unavailable
Cephradine	Orally (PO), IV,IM	15	0.9	. . .	Low serum levels after parenteral administration
Cephalexin	PO	15	0.8	Good oral absorption	. . .
Cefadroxil	PO	20	1.4	Longer serum half-life than cephalexin	Less well absorbed than cephalexin
Cefaclor	PO	25	0.7	Active against *H influenzae*	. . .

*Synthesized from cephamycin C, a fermentation product of *Streptomyces*.
†Serum half-life in monkeys.

negative *H influenzae* (cefamandole, cefaclor),[3,4] and even against *Pseudomonas* (HR756),[5] are particularly enticing.

Cephalosporins are similar to penicillins in many respects: (1) they interfere with cell wall synthesis by inhibiting transpeptidase enzyme activity; (2) they are active against Gram-positive and Gram-negative bacteria (with some exceptions, notably most cephalosporins are poorly active against *H influenzae* but effective against *K pneumoniae*); (3) they are rapidly excreted by the kidneys; and (4) they have a high therapeutic-toxic index. Indeed, the active nucleus common to all cephalosporins, 7-aminocephalos-poranic acid (Figure), resembles its penicillin counterpart, 6-aminopenicillanic acid quite closely, both containing β-lactam rings. The β-lactam moiety is adjacent to a six-membered ring in the cephalosporins and a five-membered ring in the penicillins. This apparently enhances the resistance of cephalosporins to penicillinase. Despite these similarities, cephalosporins have some properties that favor their choice over penicillins in the treatment of selected bacterial infections. These drugs are resistant to β-lactamases, active against a broad spectrum of bacterial pathogens, and are minimally cross-allergenic with penicillins.[6] There seems to be little risk to the use of cephalosporins in patients with a history of allergy to penicillin, except for those with a history of anaphylaxis or other immediate-type reactions. Cephalosporin resistance among bacterial species has not been a major problem despite the widespread use of these drugs in the community and in hospital.

Some of the pharmacologic properties of cephalosporins and their importance are listed in the Table. These include commercially available and experimental derivatives. Some of these have the advantage of an increased spectrum of antibacterial activity and good serum and tissue distribution. However, none can be trusted for the therapy of CNS infections due to the poor penetration of these drugs into the CSF. Three cephalosporins (cephalothin, cephapirin, and cephacetrile) are partially desacetylated by liver enzymes in vivo. This reduces the antibacterial activity of these drugs in vitro, but the clinical importance of this metabolic event is unclear. Further expansion of the spectrum of antibacterial activity of cephalosporins and the increasing emergence of ampicillin-resistant bacteria (mediated by β-lactamases)[7] are two factors that may increase the usefulness of cephalosporins in pediatric practice in the future. Preliminary clinical investigations have recorded the efficacy of some of the newer cephalosporins in the treatment of osteomyelitis,[8] soft tissue infections,[9] and impetigo.[10,11]

Cefaclor is a new, oral cephalosporin more active in vitro than cephalexin and cephradine against common pediatric bacterial pathogens (eg, *Staphylococcus, Streptococcus, Haemophilus,* and some enterobacteriaceae).[4] It has potential usefulness, therefore, in the treatment of many bacterial infections in pediatric patients. This potential has been tested on infants with otitis media, and the results are reported elsewhere.[12] Therapy with oral cefaclor, 60 mg/kg/day, in four divided doses was as successful as previously reported studies with ampicillin, amoxicillin, and combinations of penicillin or erythromycin with sulfonamides. These results are encouraging in that a useful drug has been added to our therapeutic armentarium. However, the study also shows the difficulty of diagnosis of otitis media, the problems of therapeutic failures and relapses, and the lack of patient compliance. Although the entire importance of some of the in vitro measurements is unclear, their variability is disturbing. For example,

Haemophilus susceptibilities to cefaclor can be as high as 5 μg/ml minimal inhibitory concentration and 20 μg/ml minimal bactericidal concentration, and peak plasma concentrations range from 1.2 to 23.4 μg/ml. This shows the erratic absorption of oral antibiotics and suggests the possibility that some patients with *Haemophilus* otitis media may have suboptimal middle ear drug concentrations. *Haemophilus* and *Streptococcus* species cause most otitis media in patients up to 9 years of age.[13] I second Dr Nelson's sage advice for further testing of cefaclor in this disease. Although a single drug is preferable, the presence of β-lactamase-producing *Haemophilus* may require the use of combinations of antimicrobials.[14] Studies of the therapy of otitis media due to these bacteria need to be carefully controlled and evaluated clinically and bacteriologically before and after therapy.

The cephalosporins are searching for a "first-line" role in the therapy of pediatric bacterial infections. Currently, pediatricians can choose cephalothin, cefazolin, or cephradine for the parenteral treatment of non-CNS infections due to sensitive bacteria other than *H influenzae*, and cefamandole for those due to *Haemophilus*. Their oral counterparts are cephalexin, cephradine (for infections that are not *H influenzae*, and cefaclor, respectively. Many clinicians will reserve this approach for patients with a history of an immediate-type penicillin-allergic reaction. Since they are resistant to hydrolysis by β-lactamase, newer cephalosporins may be useful in the therapy of ampicillin-resistant *Haemophilus* infections. However, consideration of several other alternatives also seems warranted. These include erythromycin/sulphonamide, cotrimoxazole (sulfamethoxazole/trimethoprim), cephalosporins in combination with sulfonamides, and chloramphenicol.[14] In the meantime, pediatricians would be well advised to consider the cephalosporins with cautious scepticism. Despite apparent advantages, these drugs can be very expensive, and treatment failures and a wide array of undesirable effects (phlebitis, rashes, serum sickness, anaphylaxis, elevations in serum alkaline phosphatase levels, positive Coombs' test, suppression of in vitro lymphocyte reactivity, etc) have been reported.[15,16] Doubtless, the indications and limits for cephalosporin therapy of pediatric bacterial infections will be better defined in the future through continuing analysis of bacterial trends (ie, pathogenicity and resistance) and controlled investigations comparing new products with those already familar to us. For the present, there are few situations in pediatric infectious diseases (other than in the penicillin-allergic child) where cephalosporins offer clear advantages over alternate antibacterial agents.

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Nonproprietary Names and Trademarks of Drugs

Cefazolin sodium—*Ancef.*
Cephalexin monohydrate—*Keflex.*
Cephaloglycin dihydrate—*Kafocin.*
Cephaloridine—*Loridine.*
Cephalothin sodium—*Keflin.*
Cephradine—*Anspor, Velosef.*
Cephapirin sodium—*Cefadyl.*

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Infant Tracheostomy

A New Look With a Solution to the Difficult Cannulation Problem

Howard C. Filston, MD; Dale G. Johnson, MD; Robert S. Crumrine, MD

• **Although most infant airway and ventilatory problems will be best solved by the use of endotracheal tubes, clear-cut indications for tracheostomy exist. Past reticence to use tracheostomy for infants has been due mainly to the fear of decannulation problems. Recognition of obstructive airway lesions, particularly the lumen-narrowing tracheal stomal granuloma, has been facilitated by the routine use of the newer infant bronchoscopes with optical telescopes.**

Successful decannulation begins with proper tracheostomy technique, and continues through tracheostomy management and a well-conceived decannulation program. Decannulation should include evaluation of the structure and function of the airway endoscopically and it may include translaryngeal endoscopic resection or formal surgical removal of any obstructing lesions. Experienced nursing personnel are essential to the entire program.

(*Am J Dis Child* 132:1172-1176, 1978)

Much of the hesitancy to use tracheostomy in small infants is based on the fear that tracheal decannulation cannot be accomplished once the tube is in place. Attempts at decannulation have resulted in death.[1,2] Fear of these consequences has often led to a fatal delay in establishing the tracheostomy.

This article describes the technical details we believe are important in the performance of tracheostomy and successful tracheal decannulation in small infants. Our approach is based on the belief that most of the problems in tracheal decannulation are caused by mechanical obstructions to the airway, which, when identified, can be corrected surgically. Smythe[3] recognized this problem and suggested several solutions. Success in our decannulation procedure is dependent on the technical details of the initial tracheostomy as well as on accurate diagnosis at the time of decannulation. This is accomplished through the use of relatively new infant bronchoscopes that use an optical telescope, an advance that for the first time allows clear visualization of the tiny air passages of the most premature infant.[4]

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MATERIALS AND METHODS

Indications for Tracheostomy

Without question, most infants' ventilatory and secretion-clearing requirements can be successfully managed with translaryngeal tubes, even when prolonged intubation is required. Atraumatic intubation using tube materials that have a low reactivity and that are properly sized to avoid pressure necrosis in the subglottic area will result in an acceptably low incidence of complications. Definite indications for tracheostomy do remain, however. Just as the incidence of complications with translaryngeal tubes has been reduced by greater knowledge and attention to technical details, so too can tracheostomy be made an acceptably safe procedure for the infant who requires such support.

Congenital or acquired upper airway obstructions that do not allow the use of translaryngeal tubes are clear indications for tracheostomy. When surgical procedures on or near the airway run the risk of obstruction of the airway, tracheostomy is essential.

Less clear indications for tracheostomy are instability of the translaryngeal tube and the need for prolonged translaryngeal intubation. In an occasional baby, translaryngeal tubes seem to be difficult to maintain and frequent accidental extubations occur. When experienced personnel who can easily reintubate the child are in constant attendance, this state may be tolerated. If, on the other hand, these occurrences frequently result in a respiratory arrest, tracheostomy may be a better solution.

The duration implied by the term "prolonged intubation" has been continuously redefined. Lindholm[5] defined prolonged endotracheal intubation as periods longer than 24 hours. In Lindholm's study, 12 of 55 children required secondary tracheostomy, five of these due to respiratory obstruction after endotracheal extubation. Infants in his series averaged 75 hours of intubation, with a range of 24 to 504 hours. Complication rates of 22% and 29% due to prolonged endotracheal intubation were reported by Striker et al[6] and Hatch,[7] respectively, and 32% due to tracheostomy were reported by Aberdeen.[1] If fatalities are compared, five of 62 children (8%) who died as a direct result of complications during the endotracheal intubation period were reported by Aberdeen and Glover,[8] and they attributed a 2.1% fatality rate to tracheostomy. More recently, large numbers of newborns and especially premature newborns have tolerated weeks and months of translaryngeal intubation with a seemingly low incidence of airway injury. Each institution caring for large numbers of newborns with respiratory problems must look critically at its own results and techniques and define for itself the indications for resorting to tracheostomy when an obvious need for long-term intubation exists. We would only caution that the considerable tolerances of the premature newborn to prolonged translaryngeal intubation may not be applicable to the more active older infant.

Finally, an occasional infant will not tolerate a translaryngeal tube large enough to allow adequate suctioning of secretions. When such a state exists and progressive pulmonary deterioration is occurring, tracheostomy may greatly improve the child's management.

We are not advocating the widespread use of tracheostomy. It is a procedure associated with definite hazards. Our own series presented here includes only 31 tracheostomies in six years, most of them for obstructing lesions of the upper airway. During the same period, hundreds of newborns were managed through prolonged respiratory distress problems with translaryngeal tubes. The following gives the indications for tracheostomy in our series:

Congenital airway obstructions	7
Surgical procedures about airway	1
Postintubation laryngeal or subglottic stenosis	8
Unstable endotracheal tube	3
Prolonged intubation for ventilatory support	12

Only 12 of the 31 patients had tracheostomy performed because of the anticipated need for prolonged ventilatory support. Seven of these were infants older than 1 month of age. Most were infants with complex, multisystem management problems with complicated courses after repair of major congenital anomalies. Eight infants required tracheostomy because of postintubation subglottic stenosis.

Tracheostomy Technique

Many of the points relating to the establishment of the tracheostomy and the importance of using the plastic tubes specially designed for infants have been previously discussed by others.[1,9,10] However, successful decannulation *begins* with a properly performed tracheostomy. This requires careful attention to minute details and so the entire technique is reviewed here.

If the baby is not already intubated, oral endotracheal intubation is performed, and if the infant's general condition warrants, general anesthesia is used. We generally use halothane, nitrous oxide, and oxygen with assisted respirations. Only when the infant is very unreactive does local anesthesia provide an operative field that is stable enough for a safe, well-controlled procedure.

A small roll should be placed beneath the child's shoulders and the head allowed to fall back gently. Extreme extension should be avoided, however, as this will pull the thoracic trachea up into the neck and result in a stoma that is too low. Extubation may then occur when the head is flexed.

A small (1.5 to 2.0 cm) transverse incision is placed one finger's breadth above the sternal notch. It is deepened transversely through the platysma, and then the remaining dissection is completed in the midline in a sagittal plane between the strap muscles and through the pretracheal fascia. Great care must be used as each level is dissected to assure that the trachea remains in the midline and is not pulled to one side by the retractors. Palpation for the trachea above the incision helps to locate it. The isthmus of the thyroid should be identified. If necessary, its inferior attachment to the trachea can be freed from the trachea and gently retracted cephalad.

Once the trachea is identified, its anterior surface should be cleaned to allow placement of two silk sutures as far laterally as possible directly into the tracheal rings. These sutures will be of aid subsequently in replacing a tube that has become dislodged. By pulling these sutures apart (toward the shoulders), the stoma will be opened and the trachea elevated toward the surface.

A midline tracheal incision is then made that is slightly longer than the diameter of the proposed tube. Although experimental work of Mendez-Picon et al[11] suggests that a horizontal incision that does not divide any cartilage may be preferable, we have used a vertical slit successfully. Two or three tracheal rings are usually divided, avoiding the cricoid and the thyroid isthmus. No tracheal cartilage is removed. This point is extremely important. Removal of a cartilage segment may result in subsequent instability with tracheal collapse and failure of decannulation. The incision should be tailored to admit the tube easily. If the tube has to be forced in or the stoma spread with an instrument, tearing of the stoma may result, again interfering with subsequent decannulation.

A plastic tracheostomy tube, tissue tested to ensure against the presence of organic toxins, is then inserted.[9] A tube of proper size will fill most of the tracheal lumen but will enter without friction or the need for undue force. Prior to insertion of the tracheostomy tube, the oral endotracheal tube is withdrawn by the anesthesiologist until its tip can just be seen at the superior margin of the stoma. At this point, the infant must have spontaneous respirations and the endotracheal tube must not be totally withdrawn until the tracheostomy tube is securely in place.

Placement of the tube is facilitated by moistening it with sterile saline solution. Initially, the tube is inserted from the side, allowing its narrowed anteroposterior diameter at the tip to slide easily into the vertically slit stoma. The tube is then rotated 90° to the proper alignment. Cloth tape ties secure the tube around the neck. Roentgenographic assurance that the tip of the tube is above the carina is mandatory. The tube may have to be shortened in an occasional baby. Bleeding should be negligible. If the incision is of proper size, no closing sutures will be required.

Tracheostomy Care

Continuous mist using sterile water or dilute concentrations of saline solution must be delivered through plastic tracheostomy tubes since they have no inner cannula to facilitate cleaning. Although ultrasonic aerosols of physiologic saline have been implicated in the deterioration of blood gas values and an increase in airway resistance,[2,12,13] they may be beneficial to the baby with aspiration pneumonia or thick secretions. Lindholm[5] has emphasized that ultrasonic mist has virtually eliminated death from inspissated secretions in endotracheal tubes. If adequate mist and frequent *gentle* suctioning are provided, the tube remains very clean. The tube is changed weekly. The lateral retention sutures should be removed at the time of the first weekly tube change to avoid gran-

uloma formation around them. After a few weeks of adaptation to the tracheostomy, many older infants will tolerate moderate periods without mist. Some mist is needed each day to avoid excessive desiccation of the respiratory epithelium.

Moistening of the tube prior to each insertion is extremely important. If this is not done, the tube may adhere to the skin of the stomal tract as it enters. The skin rolls in and obstructs the trachea, with resultant inability to force the tube into the tracheal lumen. If the tracheostomy tube cannot be replaced, the airway can be reestablished by endotracheal intubation until the stoma can be cleared. The importance of a nursing staff experienced in tracheostomy care cannot be overstated. The child with a tracheostomy must never be unattended. Functioning suction equipment must always be available. Until a stable tract is formed, a child with a tracheostomy should be maintained in an intensive care setting. This usually requires seven to ten days after the procedure.

Tracheal Decannulation

When the need for the tracheostomy has passed, extubation can almost always be achieved if a carefully thought-out program is followed. Initial laryngoscopy and bronchoscopy with the newborn (3 mm) bronchoscope with optical telescope (Fig 1) ensure that the airway is open, that no laryngeal or subglottic stenosis exists, that the cords function normally, and that the distal airway is clean, open, and *free of secretions.*

The tracheostomy tube is removed and the stoma carefully inspected with the bronchoscope, searching for evidence of a granuloma at its inner superior margin. A granuloma is easily recognized if present (Fig 2). Reinserting the tracheostomy tube with the bronchoscope in place may show an otherwise unnoticed granuloma. If no granuloma is present, the tracheostomy tube is replaced, the child allowed to awaken from anesthesia, and the tube then removed in the recovery room or the intensive care area with provisions for adequate prolonged observation. Usually, rapid functional closure of the stoma and continued patency of the tracheal lumen are achieved. Some infants are very upset when decannulation is performed, perhaps due to a temporary uncoordinated inspiratory effort. Sedation with morphine sulfate, 0.05 mg/kg, may prove quieting. One must be sure, however, *that the restlessness is not due to hypoxia.* Assessment of arterial blood gas levels will resolve any doubts. Allowing the baby to suckle may also help to quiet his anxiety.

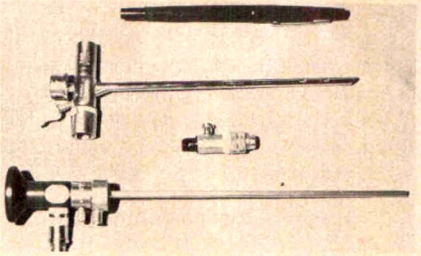


Fig 1.—Infant optical telescopic bronchoscope. Standard pen for size comparison (top); infant 20 cm × 3.5 mm bronchoscope and light source (center); 2.7 mm OD rod-lens telescope with fiberoptic light source contained within (bottom) (from Filston and Izant[15(p67)]).

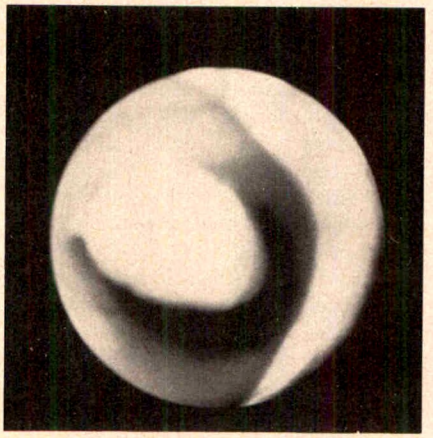


Fig 2.—View of tracheal stomal granuloma through infant telescopic endoscope (from Filston and Izant[15(p69)]).

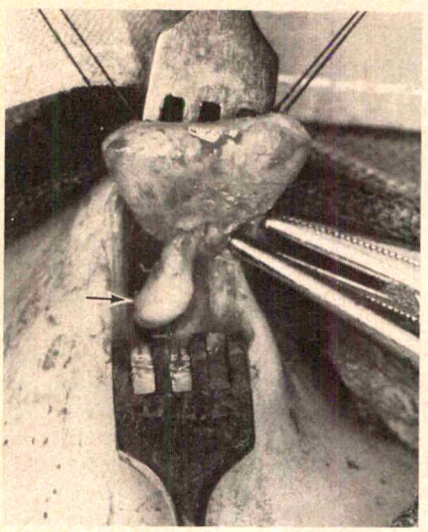


Fig 3.—Tracheostomy stoma being excised in continuity with intraluminal granuloma (arrow) (from Filston and Izant[15(p70)]).

If a granuloma is present, two approaches have been successful. If the surgeon is experienced in the use of the newer infant optical resectoscopes, the granuloma can be removed by endoscopic resection.[10] This is particularly useful for smaller granulomas. Once the mucosa has healed, extubation is attempted and is usually successfully managed as described previously where no granuloma is initially found.

For the surgeon inexperienced in the translaryngeal use of the infant resectoscope, direct surgical removal of the granuloma with formal closure of the stoma will achieve decannulation in a high percentage of cases. The operative technique is as follows: The child is intubated with an oral endotracheal tube and general anesthesia is achieved. The tracheostomy tube is removed and the neck is cleansed with antiseptic solution and draped with sterile linen. A transverse elliptical incision is made in the skin around the stoma and carefully deepened through to the trachea. The stoma is essentially "cored out."

When the trachea is identified, the dissection is continued meticulously toward the stoma until the actual edge of the original incision in the trachea itself is identified. The stomal scar tissue is cleaned from the entire edge of the incision. The external stomal tract now exists as a tube-like projection within the original tracheal incision and *in continuity* with the granuloma on the inner superior margin of the stoma in the trachea itself. Using a small, narrow dental dissector or a similar instrument, careful separation of the stomal tract from the edge of the tracheal incision is achieved. This dissection is continued on the underside of the superior margin of the stoma until the granuloma is separated from the tracheal inner wall (Fig 3).

The granuloma then can be lifted out easily with the attached contiguous stomal tract, leaving a clean tracheal incision *and lumen.* Gentle probing of the tracheal inner wall above the stoma with a small, curved mosquito hemostat will assure that all the granuloma has been removed. If any doubt exists, repeated bronchoscopy should be performed prior to completing closure.

Since the original incision in the tracheal wall was a simple vertical slit, what remains is a clean-edged elliptical tracheal stoma. This is then easily sutured closed with four or five simple sutures of 4-0 catgut. This restores the structural strength of the tracheal "arch" at the stoma site and helps to prevent collapse inward with deep inspiration. Layered closure of the strap muscles and fascial tissues in the midline with chromic catgut further supports the airway. The skin is

usually left open and packed with a small wick soaked in antiseptic solution to obviate subcutaneous infection. It closes readily after the packing is removed a few days later.

The child is then allowed to awaken from anesthesia before extubation. If he is too agitated, he is given morphine sulfate, 0.05 mg/kg, as described previously. It is important to reemphasize here that one must be sure the agitation is not due to hypoxia. Again, having provided for prolonged nursing and medical observation, the endotracheal tube is removed and the child is carefully observed. Adequate mist therapy must be continued to provide continued liquidity of tracheobronchial secretions.

Postdecannulation Management

The child is gradually weaned from mist therapy over the next several days. Occasionally, reintubation and suctioning through an oral endotracheal tube may be required if the secretions prove more tenacious or abundant than anticipated. After each suctioning episode, hyperventilation with 100% oxygen is performed and the tube again removed. When the child's condition is well stabilized and he is ready for discharge from the hospital, bronchoscopy is again performed to ensure that no new granuloma is forming at the stomal closure site. This is usually done one week after extubation. Once recovered from this procedure, he can be safely discharged home.

RESULTS

The following gives a summary of our group of 31 patients managed by these techniques:

Tracheostomies performed (N = 31)
- Age range, 1 day to 11 months
- Weight range, 1,720 to 7,900 g

Tracheostomies removed (N = 23)
- By simple removal, 13
- By formal operative excision of granuloma, 7
- By endoscopic resection of granuloma, 3
- Age range, 2 to 36 months
- Number 6 mo old or less, 12
- Weight range, 2,900 to 13,000 g
- Number 6 mo old or less, 12

Deaths, 8

Tracheostomy-related deaths, 3

Complications
- Of establishing tracheostomy, 0
- Of closure procedure (pneumomediastinum), 1

Decannulation difficulties (N = 2)
- Due to tracheal obstruction, 0
- Length of delay (range), 2 to 12 months

Analysis of Tracheostomy Duration

Reason for Tracheostomy Remaining	No. of Patients	Duration Range, mo
Congenital obstructive airway anomalies awaiting correction	4	2-22
Airway reconstruction required due to trauma	8	3-34
Continued need for ventilatory support	9	2-24
Secretion-clearing problems	2	2-3

Twenty-three patients were successfully decannulated in infancy. There were no serious complications such as hemorrhage, mediastinal emphysema, or pneumothorax from the tracheostomy procedure. One instance of pneumomediastinum was recognized on roentgenogram after a formal surgical closure but the child remained asymptomatic. The smallest baby successfully extubated weighed 2.9 kg at the time of extubation. Thirteen infants weighed less than 6 kg. Twelve infants were 6 months old or younger when decannulated. The reasons for the continued requirement for the tracheostomy are given in the Table along with the numbers and the duration range in each category. More than half the patients required prolonged tracheostomy for complex airway anomalies and severe airway injuries that required multiple-staged surgical procedures for correction.

The other large group consisted of patients who required prolonged ventilatory support. Most of these patients had either complex congenital anomalies that required staged surgical repairs or they had severe sepsis develop with multiple system failures that usually included a "shock-lung" complication and disseminated intravascular coagulopathy. Only two infants could not be weaned when first attempted. One required recannulation for copious secretions. He was successfully extubated two months later at the age of 6 months. The older infant was recannulated because he again required ventilatory support. He was decannulated at the age of 21 months. Thirteen patients were extubated successfully without formal surgical closure of the tracheal stoma when no granuloma was present. None required reintubation or subsequent formal closure. Ten patients had recognizable granulomas at the stomal site and were successfully extubated after either endoscopic resection or formal surgical closure. Several of these subsequently required brief oral reintubation for secretion-clearing therapy. No child has had a subsequent granuloma develop at the closure site nor have any patients had problems of airway obstruction related to the tracheostomy or its closure procedure after discharge. Eight patients died before attempted extubation; of these, five died from their complex primary diseases. Three deaths can be ascribed to airway complications and thus, at least in part, to the tracheostomy. One child had had extensive repair of a common tracheoesophagus that extended to the bronchial level. Granulation tissue in the repair led to obstruction of the airway below the tracheostomy tube. The one child whose death was clearly related to tracheostomy vomited a feeding and aspirated into his tracheostomy while briefly unattended in the hospital.

Seven of our patients have been sent home with tracheostomies for varying periods of time. An extensive educational program is provided for the parents so that they are well qualified in all phases of tracheostomy care prior to the child's discharge from the hospital.

COMMENT

Both emergency and elective tracheostomies have been made safe, highly valuable procedures for even the premature infant by the use of refined surgical techniques. The newer polyvinyl chloride and Silastic tubes and the superior evaluation of the tiny infant trachea provided by the optical system of the newborn bronchoscope with optical telescope contribute to this success.

Better understanding of the structure and function of the airway has led to improved approaches for decan-

nulation. Methods that have been successful in older children and adults have proved to be unsatisfactory for infants. The smallest tube available occupies so great a part of the infant's airway that the frequently used program of progressively smaller tubes and partial "corking" of the tube lumen, usually successful for older (larger) patients, will rarely be successful in infancy. The narrowing of the airway will always increase resistance. Work of breathing will increase and the infant will fatigue. Laryngeal or subglottic stenosis has been seen after even short periods of oral or nasal endotracheal intubation. The upper airway must be proved normal by inspection through the bronchoscope before attempting tracheal extubation.

The inspiratory collapse that occurs in the infant's trachea after removal of a tracheostomy tube is rarely due to "tracheomalacia" as has been alleged in the past. More often a lumen-narrowing granuloma is present on the inside of the trachea at the superior margin of the stoma. In our series, approximately 50% of the infants have had substantial granulomas.

Murphy and Popkin[14] have discussed alveolar fibrosis after prolonged assisted ventilation as another cause of tracheal collapse that may interfere with extubation. This may have been part of the problem in one of our extubation delays.

Recognition of the frequent presence of a stomal granuloma and its effects on the airway during deep inspiration has led to the development of a stepwise program for definitive treatment of the granuloma with formal surgical closure of the tracheal stoma. This program assures that extubation can be achieved with a high success rate in even the tiniest infants. Despite the improved success with this program, tracheostomy remains a hazardous procedure and must be reserved for those infants in whom clear-cut indications for its use are present. Our 10% tracheostomy-related mortality emphasizes this hazard and points up the need for conscientious, experienced nursing care in the management of the infant immediately after tracheostomy and after decannulation.

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Benefits of Learning Experience and Human Contact

The following are excerpts from the budget of the Rochester School District (English as she is spoke?):

"The immediate goals relate to creating a learning environment for children to accommodate the diversity inherent in groups of children. The program focuses on the cognitive area and also includes activities related to the affective domain which stresses the ability to relate to other human beings and to cope with one's feelings."

"Academic remediation coupled with realistic application of learning experience is reinforced by placement at viable work sites whenever feasible and wherever practical."

"The World of Work Program implements the hypothesis that a paid work experience will motivate an out-of-school youth to return to school."

Rochester Democrat and Chronicle, July 24, 1978

Xeroradiography in the Evaluation of Acquired Airway Abnormalities in Children

Nancy S. Rosenfield, MD; Dorothea R. Peck, MD; Robert M. Lowman, MD

• **Xeroradiography of the neck was performed on 36 children with suggested or known acquired tracheal abnormalities. The information obtained from the lateral projection xeroradiograph was superior in selected cases to the conventional soft tissue roentgenogram. In these cases, the information obtained justified the increased (12-fold) radiation exposure and obviated the need for positive contrast examination. This procedure should be considered in any case in which a fluoroscopic contrast examination is indicated.**

(*Am J Dis Child* 132:1177-1180, 1978)

Obstructive lesions of the airway in children should be detected quickly, painlessly, and with as little radiation as possible. Xeroradiography has proved to be useful in the evaluation of soft tissue abnormalities because of the edge enhancement effect.[1-3] Therefore, its use has been recommended in the study of tracheal abnormalities both in adults[2-6] and in children.[7-12] In this study, xeroradiography of the airway in 36 pediatric patients was used to determine (1) the value of the xeroradiograph of the neck compared with conventional soft tissue roentgenogram, (2) the comparative radiation exposure of these two procedures, and (3) the ability of the xeroradiograph to replace tomography and positive contrast studies of the airway in children.

MATERIALS AND METHODS

Medical records of 36 children who have had xeroradiography of the neck were reviewed retrospectively. The xeroradiographs and conventional soft tissue lateral roentgenograms were compared with regard to the effect on subsequent clinical management. The radiation exposure involved in each technique was calculated.

The xeroradiograph was made in both anteroposterior (AP) and lateral projections; the negative mode (in which bone is white) was usually used for both views. The following exposure factors were used: kilovolt (peak) 120, charge D, development charge C, and a distance of 91 cm. The milliampere seconds varied with the age of the child and was slightly greater for the lateral than for the AP view. As short an exposure time as possible (about one thirtieth of a second) was used to minimize blurring due to motion.

RESULTS

The 36 children examined ranged in age from 10 days to 13 years. Xeroradiography of the airway was performed for three suggested diagnoses; the yield of abnormal xeroradiographic examinations in each group is given in Table 1.

The xeroradiograph was able to delineate the airway and depict clearly the normal structures from the nasopharynx to the carina (Fig 1). Xeroradiography demonstrated both soft tissue masses (Fig 2) and long strictures (Fig 3), localized lumps of granulation tissue impinging on the tracheal lumen (Fig 4), delineated tracheostomy sinus tracts (Fig 5), and identified the position of tracheostomy tubes (Fig 3). Airways with metal tracheostomy tubes in place could not be imaged with the positive mode.

The additional information obtained from the xeroradiograph compared to the standard roentgenogram is given in Table 2. In 14 of the 21 patients with tracheal abnormalities, routine soft tissue lateral neck roentgenograms were available for comparison. The xeroradiograph provided information that was not on the lateral soft tissue roentgenogram in ten of these patients. In seven patients, the xeroradiograph demonstrated tracheal abnormalities where no comparison soft tissue lateral neck x-ray film was available. The added information from these studies was obtained from the lateral xeroradiograph only. The AP xeroradiographic view was not found helpful in this study. The lateral xeroradiographic

Table 1.—Yield of Xeroradiograph in Each Patient Group

Group	No. of Cases	Abnormal Xeroradiograph	Normal Xeroradiograph
Airway stenosis after intubation or tracheostomy	22	20	2
Upper airway obstruction*	9	1	8
Bronchial lesion	5	0	5
Total	**36**	**21**	**15**

*Patients who had not had intubation or tracheostomy.

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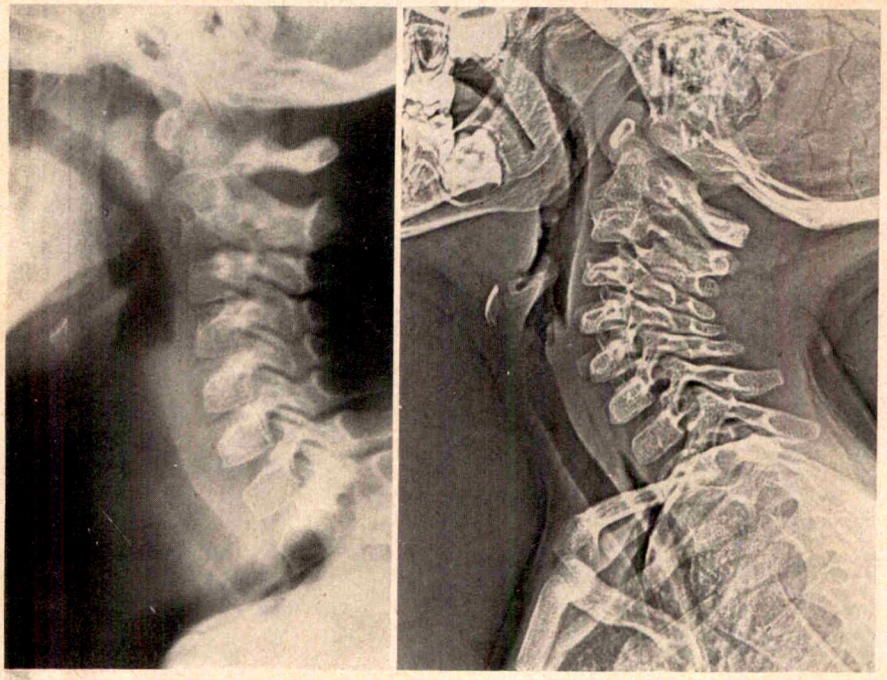


Fig 1.—Left, Normal lateral soft tissue neck roentgenogram of 2-year-old child. Right, Normal lateral xeroradiograph of neck of same-age child. Note clarity of soft tissues due to edge enhancement effect and note visualization of intrathoracic trachea.



Fig 2.—Lateral xeroradiograph of neck of 10-year-old boy. Mass is seen in retropharyngeal region (arrow). At surgery, hyperplastic lymphoid tissue was removed.

view was most helpful in revealing strictures at the level of the upper thoracic spine (Fig 3) and localized lumps of granulation tissue (Fig 4). Although in four cases the standard soft tissue roentgenogram demonstrated the existent abnormalities, the lesions were more clearly delineated on the xeroradiograph due to the edge enhancement effect.

There were no false-negative or false-positive xeroradiographs. Nineteen of the 36 patients had direct bronchoscopy. Eighteen of these were proved to have tracheal abnormalities, and one was proved to have a normal trachea. Follow-up observations have not disclosed any false-negative or false-positive cases among the remaining 17 patients.

A comparison of radiation exposure from the two procedures is given in Table 3. The exposure was approximately 12 times higher from the xeroradiograph than from the conventional roentgenogram.

COMMENT

Xeroradiography is a photoelectric method of processing a roentgen image. Adaption of a xerographic process for radiology was initiated about 25 years ago and further developed by many workers, including Roach and Hilleboe[13] in the 1950s and later, Ruzicka et al.[14] The process was substantially improved and made generally available by the meticulous work of Wolfe[15] with the technical support of the Xerox Corporation.

In xeroradiography, the x-ray image is produced on a photoconductive plate instead of on film. This photoconductive plate is made of selenium and charged to 10,000 to 14,000 V just prior to use. Exposure of the plate to roentgen rays alters this charge in proportion to the intensity of the transmitted radiation. The exposed plate is placed in a chamber containing highly charged powder (blue is used conventionally) that is attracted to the plate in proportion to the charge. The powder image is then permanently transferred to paper. Conventional x-ray machines are used for xeroradiography, and approximately the same exposure is required as for a nonscreen roentgenogram. If a thick object for which intensifying screens are needed is examined, xeroradiography requires significantly more exposure than does conventional roentgenography.[1]

Although developed primarily for mammography, xeroradiography has certain unique properties that render it valuable for other roentgenographic studies.[15] Xeroradiography provides greater contrast between soft tissue structures that differ only slightly in density than does ordinary film. In addition, in xeroradiography an edge effect is produced at boundaries of discontinuous structures. At these boundaries the toner (charged powder) is attracted in greater amounts due to the electrostatic effect. Consequently, deposition of toner is depleted outside this boundary, with resultant enhancement of the edge of the structure. In addition, there is a greater latitude of exposure with xeroradiography than with ordinary film. These factors contribute substantially to the delineation of the airway in xeroradiography of the neck.

One limitation of xeroradiography that has not been stressed previously is the inability to image tracheas with metal tracheostomy tubes in place using the positive mode. The high-density boundary of the metal attracts so much of the charged powder that adjacent soft tissue structures



Fig 3.—Top, Lateral xeroradiograph of neck of 3-year-old boy. Area of stenosis (arrow) is seen distal to plastic tracheostomy tube. Center, Standard soft tissue neck roentgenogram in same child. Tracheostomy tube is seen, but trachea distal to tube is obscured by patient's shoulders. Bottom, Xeroradiograph of another boy, aged 1 year, showing long tracheal stricture (arrows).

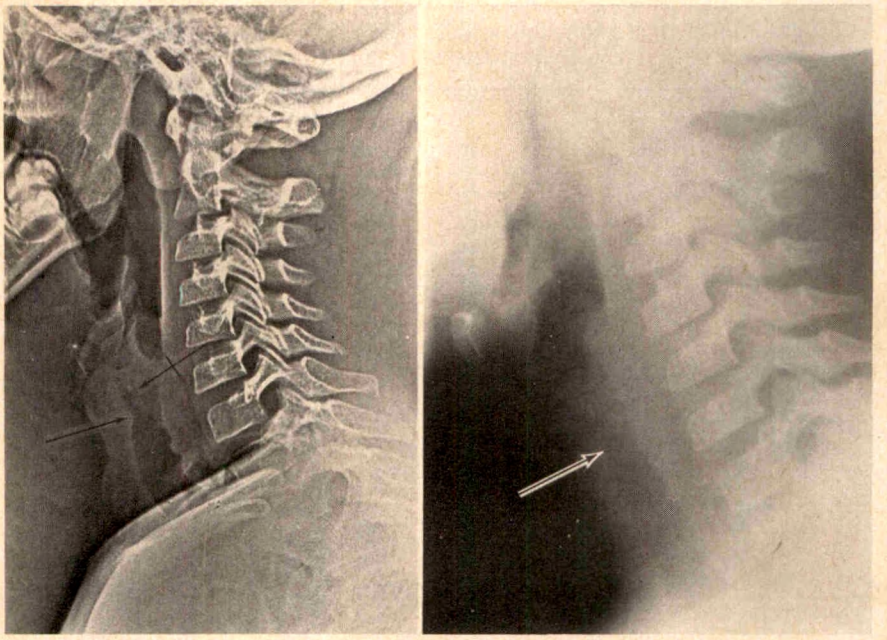


Fig 4.—Left, Lateral xeroradiograph of 6-year-old boy. Localized lump of granulation tissue in subglottic region of trachea is shown (arrow). Soft tissue web across tracheal lumen is also demonstrated (crossed arrow). Right, Standard roentgenogram of same boy's airway shows granuloma (arrow), but web is not seen.

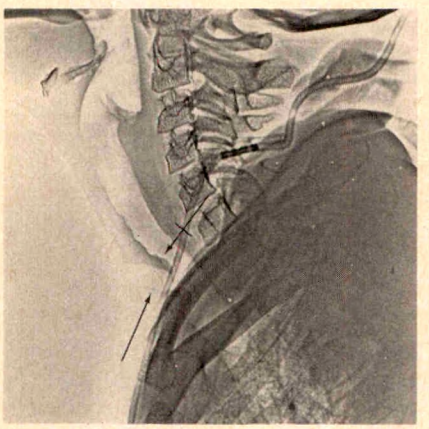


Fig 5.—Lateral xeroradiograph of 9-year-old girl. Tracheostomy sinus tract (arrow) and granuloma above it (crossed arrow).

are obscured. Therefore, in patients with tracheostomies, it is preferable to remove the tube at the time of the exposure if at all possible and if an otolaryngologist can accompany the patient. If not, a plastic tracheostomy tube may be left in place.

We found the xeroradiograph to be most helpful in those patients in whom there was a strong suggestion of airway abnormality, for example, in a patient in whom there was respiratory difficulty after tracheostomy. Complications of tracheostomy include the formation of masses of granulation tissue or the production of stenosis.[11,16,17] The incidence of these complications has varied in previous reports from 2% to 26% of all tracheostomies.[11,16,17] Some authors have stressed the value of the conventional lateral soft tissue x-ray film of the neck in delineating these abnormalities,[16,17] but Jing[18] has found that the conventional lateral soft tissue roentgenogram of the neck may not provide adequate detail for some airway structures. Therefore, in the past, many patients have had to undergo positive contrast studies of the larynx and trachea, a procedure that requires local anesthesia and fluoroscopy as well as sedation. The addition of contrast medium to an already compromised tracheal lumen is not without risk.[18] Using xeroradiography, the clarity of detail approaches that of contrast studies, and yet, sedation and anesthesia are unnecessary.[6,10] Tomography of the airway has also been advocated in adults,[18] but this is impossible in infants and small children who cannot suspend respiration for the time of the exposure.

The radiation exposure is higher with xeroradiography than with conventional soft tissue lateral roentgen-

Table 2.—Results of Xeroradiography Compared to Conventional Soft Tissue Lateral X-ray Film of Neck or Chest*

	Comparison Available (N = 36)		If Available, Does Xeroradiograph Provide More Information?	
	Yes	No	Yes	No
Abnormal xeroradiograph (n = 21	14	7	10	4
Normal xeroradiograph (n = 15)*	11	4	0	11

*Includes five patients in whom comparison was made with routine chest x-ray films since a peripheral bronchial lesion was suspected.

Table 3.—Radiation Exposure From Conventional and Xeroradiographic Studies of the Airway*

	Technique†			
Type of Study	Kilovolt (Peak)	mamp s	Focus-to-Film Distance, cm	Dose to Skin, Rads
Standard soft tissue lateral roentgenogram of neck	65-78	10-12	183	0.015
Lateral xeroradiograph of neck	120	12-40	91-102	0.180-0.480

*Calculated according to the method given in the *Radiological Health Handbook*.[23]
†2.4 mm aluminum total filtration.

ograms of the neck. In this study, the exposure was found to be approximately 12 times higher. The radiation exposure has been reported to be from six times[9] to 100 times higher.[19] However, since this examination obviates the need for positive contrast examination of the larynx with fluoroscopy and serves as an alternative to tomography, the radiation exposure is warranted by the increased information obtained. In addition, our study indicates that in children, only the lateral xeroradiographic view has proved helpful, and the radiation exposure can be lowered by eliminating the AP view. The radiation exposure from xeroradiography can also be lowered by use of the negative mode (in which bone is white) rather than the positive (in which bone is blue). The negative mode requires 30% to 40% less exposure.[4]

We can conclude, therefore, that the xeroradiographic view is warranted in the patient in whom there is a strong suggestion of abnormality and is particularly suited to children since it is a painless, nontraumatic procedure that requires no sedation. A technique introduced by McGuire[20] has recently been revised and applied to children.[21] This technique, of high-kilovoltage roentgenograms using heavy filtration, has been favorably compared with positive contrast roentgenography[22] and involves even less radiation exposure than the xeroradiograph. It remains to be determined whether the information obtained from the high-kilovoltage, heavily filtered, and magnified airway roentgenogram is as great as that from the xeroradiograph.

CONCLUSIONS

The lateral xeroradiograph of the neck provided information not available on plain roentgenograms in cases with a high index of suspicion only. There were cases in which there were localized strictures and/or collections of granulation tissue in the subglottic region. In these cases, the use of positive contrast laryngography was not necessary. The AP xeroradiographic projection added no additional information. The xeroradiograph was of no value when used as a screening procedure. The lateral xeroradiograph of the airway is indicated in any pediatric patient in whom a laryngogram is contemplated.

John Kirchner, MD, provided guidance, and he and Joan Dimow reviewed the manuscript. Thomas McCarthy and Ann Curley did photography. Gael Maher and Coreen Bentham prepared the manuscript. Stylianos Orphanoudakis, PhD, provided the dosimetry calculations.

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Mucolipidosis Type III

Multiple Elevated Serum and Urine Enzyme Activities

J. Kenneth Herd, MD; Allen D. Dvorak, MD; Hobart E. Wiltse, MD, PhD; James D. Eisen, MD; Barry C. Kress; Arnold L. Miller, PhD

• The clinical characteristics of a 16-year-old white girl with mucolipidosis type III included early growth retardation, severe dysostosis multiplex, restricted joint motion, tight indurated skin, swollen eyelids, late-onset hepatosplenomegaly, umbilical hernia, corneal opacities, and only slightly impaired mental and neurological development. Cultured fibroblasts contained numerous coarse perinuclear refractile inclusions. Biochemical findings indicated the following: (1) normal levels of urinary acid mucopolysaccharides, (2) deficient activities of multiple lysosomal hydrolases in cultured fibroblasts, (3) elevated activity levels of seven serum lysosomal hydrolases, and (4) elevated activity levels of four lysosomal hydrolases in urine.

(*Am J Dis Child* 132:1181-1186, 1978)

Mucolipidosis was first described as a syndrome distinct from Hurler's disease by DeMars and Leroy[1] in 1967. Distinction was based on the presence of a dense accumulation of highly refractile granules in the perinuclear cytoplasm of cultured skin fibroblasts from these patients when living cells were viewed with the phase microscope. The syndrome was called inclusion-cell or I-cell disease, and children with this disease bore some resemblance to the Hurler syndrome. An article by Leroy et al[2] in 1971 described persons with I-cell disease who all had normal urinary mucopolysaccharide levels.[2] As additional cases were reported,[3-12] stored materials were characterized as both mucopolysaccharides and glycolipids, which led to the classification of mucolipidoses I, II, and III.[10-13] Despite clinical differences, refractile, perinuclear, cytoplasmic inclusions in the fibroblasts and normal levels of urinary mucopolysaccharides were common to all patients with mucolipidosis.

At present, the molecular basis for mucolipidoses I, II, and III is not known. Biochemical findings that have been used to delineate the mucolipidoses include the following: (1) an absence of mucopolysaccharidiuria,[13] (2) the accumulation of greater than normal amounts of mucopolysaccharides labeled with sodium sulfate S 35 by skin fibroblasts,[8,14,15] (3) very low intracellular levels of several lysosomal enzymes within the cultured fibroblasts,[16-20] (4) elevated levels of several of the same enzymes in the culture medium[21] and serum,[14,18,19] (5) decreased endocytosis of certain lysosomal hydrolases,[22,23] and (6) abnormal electrophoretic mobilities of one or more lysosomal enzymes.[19,24-26] Although most of these biochemical findings are attributed to mucolipidosis II or III, a biochemical distinction specific for either mucolipidosis II or III remains to be made.[27] Recently, a single case of mucolipidosis I has been reported in which stored sialic acid-containing compounds and a deficiency of sialidase (neuraminidase) were found in the patient.[28] Also, a second case of isolated neuraminidase deficiency has been reported that resembled mucolipidosis I but was biochemically distinct from mucolipidoses II and III.[29]

The clinical and biochemical characteristics common to 12 patients with mucolipidosis III have been proposed as diagnostic criteria.[30] In this article we report detailed clinical and biochemical findings of another patient who satisfied all but two of these criteria. Of particular interest was the striking elevation of several urinary lysosomal enzyme activities and their unusual instability to cold.

REPORT OF A CASE

A white girl was delivered without incident after 9 months' gestation. The mother was 27 and the father was 29 years of age; they were in good health and not known to be related. The mother's parents were from Sweden and Norway; the father's parents were from Ireland and England. The patient weighed 2.6 kg at birth and was described as a normal, active baby. Shoulder motion was not restricted and the skin was not tight. At 3 weeks of age severe diarrhea developed that required parenteral fluids and blood transfusions. Despite recurrent diarrhea in the first year, she sat at 6 months, said words at 12 months, and walked at 13 months. At 1 year of age she weighed 8 kg.

At 15 months of age, tight, indurated skin on the fingers and legs was noted. At 22 months, her weight was 9.5 kg, her length was 76.8 cm, and serum protein-bound iodine (PBI) level was 3.6 μg/dl. She was receiving thyroid therapy, 15 mg/day, which was gradually increased to 65 mg/day. Sixteen normal teeth erupted at the usual times. At 2 years, the hair was said to be coarse, the extremities were cool, and the skin was still indurated. She received routine immunizations and recovered from rubella without sequelae. Respiratory infections were infrequent.

At age 29 months, height and weight were still both less than the third percentile. Coarse facial features were observed. The liver and spleen were not enlarged. The thickened, waxy character of the skin remained. Results of a physical examination showed normal heart, lungs, eyes, ears, nose, and throat. Results of an ophthalmologic examination were normal. The patient was unable to arise unaided from the supine position because of stiff legs. Mentality seemed normal. Laboratory studies disclosed the following findings:

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urinalysis, normal; hemoglobin, 8.5 to 10 g/dl; complete blood cell count (CBC), otherwise normal; BUN, 17 mg/dl; serum electrolytes, normal; PBI, 9.0 μg/dl; ECG, normal; and urinary chondroitin sulfate, 25%. (The significance of this result is unknown since persons accountable for that analysis at another institution in 1961 were not available for interpretation of results or explanation of methods.) Roentgenograms of the hands and wrists showed "bullet-shaped" metacarpals, deformity of the distal radius, and increased breadth of the shaft of both radius and ulna; those of the spine showed anterior compression of L-1 with decreased anteroposterior dimension. Similar but less prominent changes in L-2 combined to produce a slight kyphosis at the thoracolumbar junction. Substantial valgus deformity of the femoral neck was noted. A skin biopsy specimen showed fibrosis of the corium.

During the next eight years, her pediatrician noted a small umbilical hernia, normal speech development, frequent nasal congestion, two attacks of otitis media, grade 1 to 2 functional systolic heart murmur, no corneal clouding, and unsuccessful smallpox vaccination. When the patient was 9 years old, her IQ was 80-90. At 10 years and 2 months of age, cardiacthoracic ratio was 0.635, she weighed 13.6 kg, and she was 84.5 cm tall.

At age 13 years and 2 months, the following characteristics were noted: The upper segment-lower segment ratio was 1.3. The short, thickened fingers had flexion contractures at all joints. The nose was small with decreased cartilage, and the patient had thickened lips and prominent brows suggestive of Hurler's syndrome. Mild hepatomegaly, but no splenomegaly, was present. An EEG showed mild left ventricular hypertrophy. Fine opacities were seen beneath the corneal epithelium on slit-lamp examination by an ophthalmologist. The maculae were normal. Roentgenograms showed a normal skull, beaking of the inferior edge of several vertebral bodies, flattening of the femoral heads, valgus angulation of the femoral neck, flared, small iliac wings, flattened proximal tibial epiphyses, and shortened clavicles. Results of tests for urinary mucopolysaccharides were normal. Studies of skin fibroblasts showed a normal 46XX chromosome complement. The cultured skin fibroblasts showed dense accumulations of highly refractile granules scattered throughout the cytoplasm when examined with phase-contrast microscopy. These granules were localized to the perinuclear cytoplasm in the patient's cells, whereas smaller numbers of similar granules were distributed throughout the cytoplasm of normal control fibroblasts. Granules in the patient's fibroblasts did not show metachromasia when stained directly with toluidine blue.[11] The diagnosis of mucolipidosis was compatible with the clinical course.

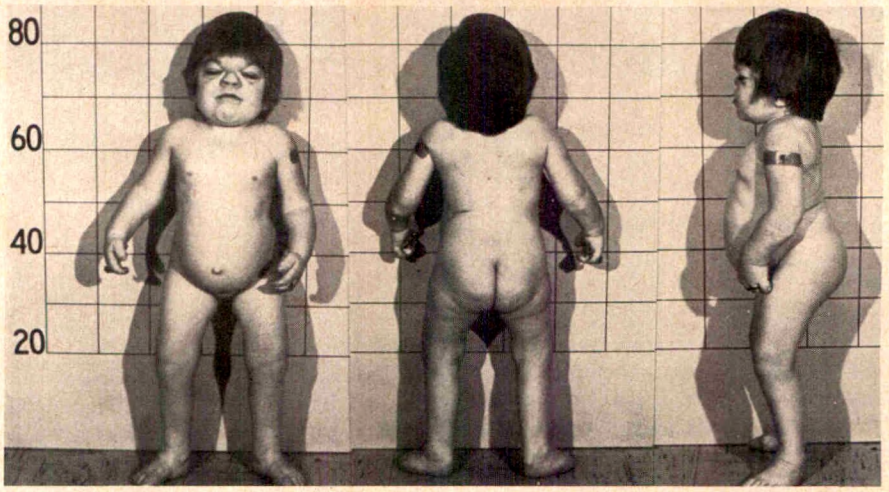


Fig 1.—Age, 16⅓ years. Height, 87.6 cm. Notice dwarfism, protuberant abdomen, umbilical hernia, flexion contractures of knees, hips, elbows, wrists, and fingers; flattened lumbar curve with small kyphosis; and Hurler-like facies.

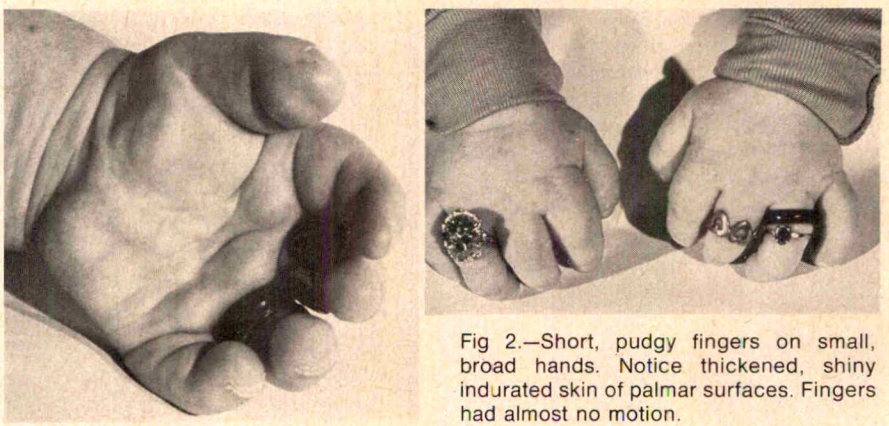


Fig 2.—Short, pudgy fingers on small, broad hands. Notice thickened, shiny indurated skin of palmar surfaces. Fingers had almost no motion.

We examined the patient when she was 16 years and 4 months old and found the following (shown in Fig 1 and 2): weight, 11.7 kg; height, 87.6 cm; and upper-lower segment ratio, 1.33. The skin had a shiny, waxy appearance and was tightly drawn over the joints; the texture was best described as brawny. Scattered senile keratoses were seen on the trunk. Telangiectatic vessels, dilated veins around the eyes, and facial acne were not seen. The scalp hair was light brown and slightly coarse; there was fine hair on the extensor surfaces of the arms and legs, and there was a small amount of coarse axillary and pubic hair. The eyelids were swollen and indurated. The mouth was broad, the lips were thickened, but the tongue was not enlarged or fissured. The gingiva were not hypertrophied and the palatal arch was normal. The teeth were of normal size and shape. Excursion of the mandible was very limited. The small, bony thorax was not misshapen; there was no palpable breast tissue. A grade 2/6 systolic murmur was heard along the left sternal border with radiation toward the apex. Radial and dorsalis pedis pulses were not palpable. No digital cyanosis was noted. Other findings included a protuberant abdomen; a 0.5-cm umbilical hernia; a nontender, firm liver edge 5 cm below the right costal margin; and a nontender, firm, sharply defined spleen 4 cm below the left costal margin. Flattening of the normal lumbar curve was evident, with a small kyphosis at L-2. Strikingly short, stubby fingers with marked flexion contractures at all joints arose from small pudgy hands. Tight flexion contractures were noted at the wrists, elbows, shoulders, ankles, knees, and hips, with substantial loss of motion. Muscle strength was normal where it could be tested. The gait was wide based, with foot sliding; she could not get her heels to the floor because of tight Achilles tendons. (The prominent roentgenographic findings when the pa-



Fig 3.—Lateral lumbar spine: Second lumbar body is hypoplastic with characteristic "beak" configuration along its inferior aspect. Posterior scalloping is seen in several lumbar vertebral bodies.

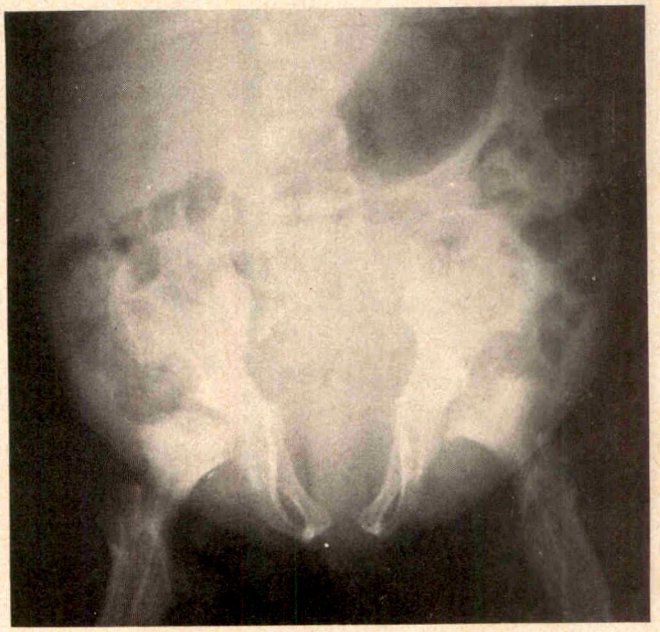


Fig 4.—Pelvis (anteroposterior projection): Iliac bones are narrow and their basilar portions are hypoplastic with slanting acetabular roofs. Pubic and ischial bones are elongated. Coxa valga deformity is present.

tient was 16 years old are shown in Fig 3 to 6.)

The patient's mental status was appropriate for her age, but she showed signs of immaturity with strong dependence on her mother. Although able to discuss her physical disability, she often changed the topic to unrelated events. Awareness of her appearance was evidenced by such phrases as "A lot of people don't think I'm a teenager." Menses had not begun. Auditory perception was acute. She had received 30 mg *United States Pharmacopeia* thyroid hormone therapy per day continuously since age 2½ years. There have been no siblings.

MATERIALS AND METHODS

A total of 720 ml of urine was refrigerated as collected at home, with thymol as preservative. Dialyzed aliquots were screened for acid mucopolysaccharides by the acid albumin turbidity and alcian blue 8GX precipitation tests.[32,33] Acid mucopolysaccharides were precipitated from the remaining urine and analyzed colorimetrically as previously described.[34] Cultured skin fibroblasts were grown from a biopsy specimen from the left deltoid area[35] and tested for β-glucuronidase activity using published methods.[36] When this test showed abnormally low levels of enzyme activity, living fibroblasts were sent to one of us (A.L.M.) and propagated identically to normal controls and known mucolipidoses II and III fibroblasts (confirmed in at least two other laboratories) according to published methods[1] with the use of Ham's F-10 media containing 15% calf serum. All cultures were harvested simultaneously five days after reaching confluency, at which time the cell number had become five times that of the inoculum. The cells were rinsed with 0.85% saline solution before they were removed from the flasks. Homogenates were prepared by sonicating a 1:10 (weight by volume) dilution of cells in glass-distilled water for 30 seconds. Assays for activity of seven lysosomal hydrolases in the homogenates of cultured fibroblasts were done according to Leroy et al[18] with the use of the appropriate 4-methylumbelliferyl (4-MU) substrates.

Urine and serum separated from freshly clotted blood were shipped frozen (−20 °C) and/or fresh (0-4 °C) to one of us (A.L.M.) for assays of various lysosomal hydrolases. Acid β-D-galactosidase (EC 3.2.1.23), *N*-acetyl-β-D-glucosaminidase (EC 3.2.1.30), α-D-galactosidase (EC 3.2.1.22), and β-D-glucuronidase (EC 3.2.1.31) were assayed using the appropriate 4-MU substrate used in published methods[18] except for acid β-D-galactosidase in urine, which was assayed at a pH of 4.0. Serum aliquots (10 μl)



Fig 5.—Right radius and ulna: Radius and ulna are broad in their shafts and tapered in their metaphyseal regions, with an angulated obliquity of growth plates.



Fig 6.—Hands: Ossification of carpal bones and epiphyses is retarded. Metacarpals are centrally thickened and second to fifth are proximally pointed. Tapering of distal phalanges and tilting of lower ends of radius and ulna toward each other are present.

were assayed undiluted, except in the instance of *N*-acetyl-β-D-glucosaminidase where a one-eighth dilution in 22 mM of citrate-phosphate (pH, 4.4) was used. The activity of α-D-mannosidase (EC 3.2.1.24) was measured according to Hultberg et al,[37] whereas α-L-fucosidase (EC 3.2.1.51) was assayed using 50 μl of 1 mM 4-MU-α-L-fucopyranoside dissolved in 100 mM of sodium citrate-citric acid at a pH of 5.0. Serum arysulfatase A (EC 3.1.6.1) activity was measured using *p*-nitrocatechol sulfate according to Baum et al.[38] All assays were done at 37 °C for 15 minutes. Aliquots of fresh urine and serum from normal subjects and from human subjects with mucolipidoses II and III were assayed as controls.

RESULTS

Results of the acid albumin and alcian-blue 8GX precipitation screening tests were negative for increased urinary acid mucopolysaccharides. Analysis of total cetylpyridinium chloride-precipitable urinary mucopolysaccharides showed the following (per gram of creatinine): uronic acid, 5.2 mg (measured by a carbazole method) and 8.6 mg (measured by an orcinol method); hexosamine, 14.9 mg; and *N*-sulfated hexosamine, 2.8 mg. These are normal values for our laboratory. On electrophoresis, a single spot was seen with mobility of chondroitin −4, 6− sulfate. The activity of seven lysosomal hydrolases, measured in sonicates prepared from cultured fibroblasts of normal controls, from our patient and from known patients with mucolipidoses II and III, is given in Table 1. In comparison with the normal controls, the following reduced levels of enzyme activity were found: acid β-D-galactosidase (34% of normal), α-D-galactosidase (20% of normal) *N*-acetyl-β-glucosaminidase (45% of normal), β-D-glucuronidase (17% of normal), and α-D-glucosidase (27% of normal). These results are similar to those found in the fibroblasts of the known patient with mucolipidosis III but are generally less severe than those found in fibroblasts of the known patient with mucolipidosis II. In contrast, α-D-mannosidase and β-D-glucosidase activities were present at normal and elevated levels, respectively, compared with the normal controls.

Accompanying the reduction of lysosomal enzyme activities in the cultured fibroblasts was an increase in all seven lysosomal enzyme activities in the patient's serum (Table 2) and an increase in five of the six lysosomal enzyme activities in the patient's urine (Table 3), compared with those of the normal controls. The increases in serum enzyme activities had a pattern that was similar to that observed in the serum of the known patients with mucolipidosis III but that was less pronounced than that observed in the serum of a patient with mucolipidosis II (Table 2). The increases in urine enzyme activities were similar to the values obtained in both the known patients with mucolipidoses II and III (Table 3).

Table 1.—Acid Hydrolase Activities in Cultured Skin Fibroblasts*

Enzyme	Normal†	Mucolipidosis Type II‡	Mucolipidosis Type III§	Patient
β-D-galactosidase	578 (304-949)	0.72	162	199
α-D-galactosidase	66 (57-88)	13.00	16	13
N-acetyl-β-D-glucosaminidase	2,406 (2,427-6,331)	424.00	607	1,087
α-D-mannosidase	18§ (6-34)	5.70	. . .	16
β-D-glucuronidase	178 (141-275)	30.00	11	30
α-D-glucosidase	56 (33-96)	22.00	. . .	15
β-D-glucosidase	41 (27-57)	53.00	. . .	73

*Nanomoles of substrate hydrolyzed per milligram of fibroblast protein per hour; single samples assayed in duplicate unless otherwise indicated.

†Mean of 50 normal samples; range in parentheses (except mannosidase).

‡Duplicate determinations run concurrently with patient analyses and within the range of all values of mucolipidosis types II and III at this laboratory.

§Mean of 15 normal samples; range in parentheses.

Table 2.—Acid Hydrolase Activities in Fresh Serum*

Enzyme	Normal†	*N*	Mucolipidosis Type II‡	Mucolipidosis Type III‡	Patient
β-D-galactosidase	6 (2-12)	8	58	32	55,85
α-D-galactosidase	11 (2-20)	8	170	24	34,56
N-acetyl-β-D-glucosaminidase	637 (401-1,408)	8	20,000	10,400	9,800;5,600;10,300
α-D-mannosidase	84 (59-100)	9	3,300	2,500	1,700;1,600;3,000
β-D-glucuronidase	11 (6-22)	9	2,000	640	360,570,630
α-L-fucosidase	320 (195-761)	9	7,200	3,900	1,700;3,000;3,400
Arylsulfatase A	29 (20-50)	4	2,000	. . .	510

*Nanomoles of substrate hydrolyzed per milliliter of fresh (unfrozen) serum per hour at 37 °C.

†Mean; range in parentheses.

‡Duplicate determinations run concurrently with patient analyses and within the range of all values of mucolipidosis types II and III at this laboratory.

Table 3.—Acid Hydrolase Activities in Fresh Urine*

Enzyme	Normal†	Mucolipidosis Type II‡	Mucolipidosis Type III‡	Patient§
β-D-galactosidase	1.70 (0.90-3.40)	4.2	3.6	3.50 (2.46-5.80)
α-D-galactosidase	0.3 (0.1-0.5)	0.8	1.4	2.5
N-acetyl-β-D-glucosaminidase	1.90 (0.60-4.40)	17.0	20.50	21.6 (15.3-46.7)
α-D-mannosidase	0.10 (0.01-0.20)	0.8	0.43	0.83 (0.72-0.90)
β-D-glucuronidase	0.31 (0.20-1.00)	0.3	0.64	0.36 (0.26-0.60)
α-L-fucosidase	0.21 (0.20-0.40)	6.0	1.81	11.0 (9.5-12.2)

*Nanomole substrate hydrolyzed per minute per milligram creatinine in fresh (unfrozen) urine.

†Mean of eight separate samples; range in parentheses. Duplicate determinations run concurrently with patient analyses and within the range of all values of mucolipidosis types II and III at this laboratory.

‡Duplicate determinations run concurrently with patient analyses and within the range of all values of mucolipidosis types II and III at this laboratory.

§Mean of six separate samples, range in parentheses.

COMMENT

The condition of children with mucolipidosis may initially be misdiagnosed Hurler's syndrome because of similar physical characteristics and roentgenographic findings. When results of tests for urinary mucopolysaccharides are normal, another diagnosis is sought. In our patient, absence of hepatosplenomegaly, late onset of symptoms, absence of mucopolysaccharidiuria, absence of mental retardation, and the presence of unusually tight skin and stiff joints led to a diagnosis of mucolipidosis. Support for this diagnosis was gained from the finding of low levels of β-glucuronidase in her cultured fibroblasts. The diagnosis was confirmed by the finding of low cellular and high serum and urine levels of several lysosomal enzymes as given in Tables 1 to 3.

We have classified our patient according to the presently available scheme for the mucolipidoses.[30] Our patient fulfilled all of the clinical criteria for mucolipidosis type III except mental retardation and valvular heart disease. Although many of our patient's characteristics were common to both mucolipidosis types II and III, her survival in relatively good health to 17 years of age and the absence of severe mental retardation exclude her from having mucolipidosis II. The severity of the skeletal changes and impaired growth in this patient were unusual for mucolipidosis III. Kelly et al[30] have demonstrated similar clinical heterogeneity among 12 patients with mucolipidosis III. Our patient bears physical and roentgenographic resemblance to the case reported by Spranger, which could not be reliably classified in the absence of enzyme studies.[39]

Additional evidence for the classification of our patient as mucolipidosis type III comes from the data in Tables 1 to 3, which indicate a multiple lysosomal enzyme deficiency in the patient's cultured fibroblasts and a concurrent elevation of the serum and urine lysosomal hydrolase activities similar to those reported for other cases of mucolipidosis III.[14,18-20,30] Besides the report of elevated arysulfatase A,[40] this is the first report, of which we are aware, of the elevation

of multiple lysosomal acid hydrolase activities in fresh urine from a person with mucolipidosis III. We have repeatedly been unable to detect elevations in all but one enzyme (*N*-acetyl-β-D-glucosaminidase) in frozen urine of either the present patient or in other patients with mucolipidosis III. This reflects the biochemical instability of these enzymes. Detailed study of the lability and kinetics of two of these enzymes isolated from 20 liters of fresh urine is currently under way in one of our laboratories (A.L.M.). Less-pronounced effects are usually found in the levels of lysosomal hydrolase activities from the cultured fibroblasts and serum of patients with mucolipidosis III when compared with similar samples obtained from patients with mucolipidosis II.[11-19] The unchanged α-D-mannosidase activity in cultured fibroblasts of our patient is similar to results obtained for other patients with mucolipidosis III[30] and could reflect the biochemical heterogeneity that exists among patients with type II and type III.[19,24,25,41] The clinical, roentgenographic, and biochemical results are most compatible with our patient being classified in the type III category.

This report should contribute to the further delineation of the mucolipidoses classification. It exemplifies the need to analyze fresh (not frozen) serum and urine samples for lysosomal enzyme activities in patients with mucolipidosis III.

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B. Hayhome, PhD, and J. Tschida gave technical assistance and John O'Brien, MD, provided laboratory facilities for the enzymological work. R. N. Shears, MD, Hutchinson, Kan, and B. Oberst, MD, Omaha, originally referred the patient to us and contributed detailed office notes.

Cultured fibroblasts of our patient may be obtained from The Human Genetic Mutant Cell Repository by writing to Arthur E. Greene, PhD, Institute for Medical Research, Copewood and Davis streets, Camden, NJ 08103. Request cell line GM 1494.

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Staphylococcal Scalded Skin Syndrome

A Complication of Circumcision

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• **Numerous complications have been reported as a result of neonatal circumcision. We describe here three cases of staphylococcal scalded skin syndrome that were thought to be due to infected circumcisions. A review of the literature failed to disclose descriptions of staphylococcal scalded skin syndrome as such a complication. In spite of recent American Academy of Pediatrics recommendations against routine circumcision, it will continue to be a common procedure. Careful preoperative and postoperative screening and guidance are urged to prevent staphylococcal scalded skin syndrome and other complications.**

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Neonatal circumcision is the most common surgical procedure in the United States today. Many complications have been reported to be associated with this procedure. Recently, we encountered two cases of staphylococcal scalded skin syndrome as complications of circumcision in otherwise healthy full-term infants. Each case had the essential clinical features of staphylococcal scalded skin syndrome. A third case, though unproved, was believed to be clinically the same.

An extensive review of the literature failed to disclose reports of staphylococcal scalded skin syndrome as a complication following circumcision. We hope to alert physicians caring for newborns to this possibility.

Over the years, when advising parents of the problems encountered after circumcision, we had not considered staphylococcal scalded skin syndrome. Indeed, we have even reassured parents as to the paucity of problems after "ritual" circumcisions.

REPORT OF CASES

Case 1.—A 13-day-old male infant was admitted because of "high fever to 40.6 °C" and generalized "peeling of his skin." Discharged on the fourth day of life, he developed two pustules in his groin and on the shaft of his penis six days prior to admission, but he was "doing fine" and thriving otherwise. Four days prior to admission, he underwent a ritual circumcision performed by a *Mohel*. The following day, more pustules developed on the lower abdomen and about the circumcision site. The mother also noted that the skin was "red," and easy to "peel off." Their pediatrician recommended immediate hospitalization.

On admission, the infant was hypothermic and in profound shock. The skin was erythematous, almost violaceous in areas, desquamating and tender. Nikolsky's sign was present. The circumcised area was red, edematous, and exuding yellow pus (Fig 1). Cultures were taken and parenteral administration of methicillin and gentamicin begun. He was treated aggressively with



Fig 1.—Case 1. Red, edematous circumcised area exudes yellow pus.



Fig 2.—Case 2. Red, edematous circumcised area is covered with profuse, thick, yellow-green exudate.



Fig 3.—Case 3. Skin never desquamated but appeared like that of early staphylococcal scalded skin syndrome.

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electrolyte solutions, whole blood, other plasma expanders, vasopressors, and mechanical ventilatory support. In spite of these, he died 41 hours after admission. *Staphylococcus aureus* was cultured from the nasopharynx, throat, pustules, circumcised area, and conjunctivae. Blood cultures were negative.

Case 2.—A full-term 3-day-old male infant was transferred to our medical center with a history of diarrhea and peeling of his skin beginning that day. On the second day of life, he was circumcised with a commercial clamp; on the third day (28 hours after circumcision), he had two explosive watery stools, and the skin of the penis, scrotum, buttocks, and periumbilical area were noted to be red and desquamating (Fig 2). The circumcised area was red, edematous, and covered with a profuse, thick, yellow-green exudate. Nikolsky's sign became positive over his entire body surface. Parenteral administration of methicillin was begun, along with fluids and electrolyte replacement. He responded well and was discharged after 13 days. *Staphylococcus aureus* grew from the cultures of the infant's nasopharynx, the circumcised area, and from the mother's nose.

Case 3.—A 4,320-g, 2-day-old male infant was transferred to our medical center for evaluation of possible sepsis. At 31 hours of age, he was circumcised with a commercial clamp. Several hours later, he was noted to feed poorly and became lethargic, febrile to 39.4 °C, and cyanotic in room air. A generalized erythematous maculopapular rash erupted. The circumcised area was obviously infected, appearing red, swollen, hot, and covered with a heavy, yellow, purulent exudate. No other site of infection was found. The usual as well as the infected sites were cultured and antibiotic therapy begun. The rash became confluent. The skin was edematous and very tender. Within two days, the rash began to fade, and by the fourth hospital day, it cleared. While the skin never desquamated, it appeared like that of an early staphylococcal scalded skin syndrome (Fig 3). The cultures from the nasopharynx and circumcision site grew *S aureus*. The infant responded well to therapy.

COMMENT

The etiology and pathophysiology of staphylococcal scalded skin syndrome were a mystery to Gottfried Ritter von Rittershain[1] when he originally described 297 cases of this entity, which became known as Ritter's disease.[1] Recently, 100 years later, it has been recognized that most cases are due to infection with *S aureus*, known to release an exotoxin, exfoliation.[2] This toxin causes a separation of the epidermis from the basement membrane at a superficial level and leads to the classical Nikolsky's sign. Other names ascribed to the condition are toxic epidermal necrolysis and Lyell's disease, the latter usually being applied to the condition in adults.

We thought that case 3 was similar to the 11 described by Melish and Glasgow[2] as a milder variant of the exfoliative form of staphylococcal scalded skin syndrome.

According to the 1971 report of the Ad Hoc Task Force on Circumcision of the American Academy of Pediatrics, "Circumcision is a surgical procedure that requires careful aseptic technique, systematized post-operative observation, and evaluation after discharge from the hospital. The immediate hazards of circumcision of the newborn include local infection which may progress to septicemia, significant hemorrhage, and mutilation."[3]

Many complications of elective circumcision are reported. Hemorrhage is the most common complication; local infection ranks second in frequency.[4] This latter complication is manifested by local inflammatory changes, ulceration, and suppuration. More severe infections have been reported, including partial necrosis of the penis, staphylococcal septicemia with osteomyelitis, and pulmonary abscesses.[5] The open wounds of circumcision have been reported as a source of neonatal sepsis in prematures.[6]

Other, although rare, complications reported include urethral fistula,[7] circumcision of unrecognized hypospadias,[4] laceration of the penile and scrotal skin,[5] wound dehiscence,[4] urinary retention from a too-tight dressing,[5] injury to the glans,[6] retention of plastic device ring with edema of the penile shaft,[8] and surgical bivalving of either the dorsal or ventral half of the glans while making the "dorsal slit."[9]

Staphylococcal scalded skin syndrome is caused by a staphylococcal exotoxin that is elaborated at the site of infection. In the three cases presented, the circumcision site was the probable focus. As reported, neonates and infants are the predominant victims for almost all cases. These patients have not demonstrated any antecedent or subsequent immunological or metabolic deficiencies.[10]

Since this disease can be rapidly fatal if untreated, as illustrated by case 1, accurate diagnosis and treatment are necessary. It is urged that careful scrutiny of the neonate's total skin surface be made prior to circumcision. This was clearly omitted in case 1. Any rash, especially pustulosis, should force the operator to delay the procedure, as should the presence of an outbreak of staphylococcal infection in the nursery.

In spite of recent recommendations against circumcision[3] except for specific medical and religious requirements, it has and will continue to be a common surgical procedure. Awareness of its potential hazards, scrupulous preoperative examination, detailed instructions to the parents regarding postoperative care, and observations for signs of complications are vital to an uneventful outcome.

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Fournier's Syndrome

Report of Three Cases and Review of the Literature

Sidney J. Sussman, MD; Ruth P. Schiller, MD; V. L. Shashikumar, MD

• Three children, aged 9 days, 3 weeks, and 9½ months, were treated for Fournier's syndrome. The portals of entry for a miscellaneous group of pathogens included a circumcision in the first, a circumcision and a diaper rash in the second, and a hot water burn in the third. The development of the condition after a circumcision is noteworthy because it is an extremely common surgical procedure. Medical and minor surgical treatment of the gangrenous areas during the period of rapid healing was successful. This approach contrasts with those researchers who recommend grafts. All three children survived, although one died three years later of complications from the original burn, and in another, one testicle could not be palpated after healing.

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Fournier's syndrome,[1-3] first reported by Baurienne,[4] is a malignant gangrenous infection of the scrotum or the penis and perineum. While Fournier's syndrome has occurred in patients from 5 days to 80 years of age,[5-16] cases have rarely been reported in children.

See also pp 1167 and 1187.

Three children with Fournier's syndrome were admitted to St Christopher's Hospital for Children during a two-month period. This is a report of these cases and a review of the literature.

REPORT OF CASES

Case 1.—This 3-week-old child had a circumcision at age 3 days. At age 7 days a diaper rash was first treated with petrolatum, a combination of zinc oxide and cod liver oil (Desitin), then nystatin. At age 17 days, severe necrotic ulcerations developed in the perineum and the base of the scrotum. The child was admitted to a local hospital, where intravenous nafcillin sodium and soaks were administered with little improvement. At age 21 days, the child was transferred to St Christopher's Hospital for Children. On admission, there were extensive gangrenous ulcerations at the base of the scrotum, tip of the penis, and in the perineum (Fig 1). There were a few vesicles in the crease of the left groin and purulent material with scabs over the knees and toes. The urinary stream was strong but thin.

Laboratory studies showed a WBC count of 21,100/cu mm, with 61% neutrophils, 25% lymphocytes, 10% monocytes, and 4% basophils. Levels for hemoglobin, IgM, IgG, IgA, and BUN were normal. Reduction of nitroblue tetrazolium was normal, and VDRL reaction was negative. Results of urinalysis were normal. Skin culture from the scrotum disclosed *Escherichia coli* and *Enterobacter cloacae*. Normal flora grew from the nasopharynx, and a blood culture was negative. A skin biopsy specimen from the infected area showed irregular acanthosis, generalized parakeratosis, mild spongiosis, and edema of the dermal papillae. The admitting diagnosis was gangrenous, necrotic ulcerative skin lesions with superinfection, cause unknown. The wound was debrided and treated with saline soaks, 0.1% gentamicin sulfate cream, nitrofurazone dressings, and heat. There was slow improvement during the seven days of hospitalization. At age 5 years, scars were present in the scrotum, and the testicles were palpated in the scrotal sac.

Case 2.—This 9-day-old infant had a circumcision at age 3 days. Shortly thereafter, the scrotum became erythematous and was treated with baby powder and then creamed cornstarch and petrolatum jelly. Erythema rapidly progressed to gangrene, and on the eighth day the wall of the scrotum sloughed. Purulent material developed around the scrotum, and the left flank became erythematous. Throughout this, the infant did not appear ill. He was admitted to St Christopher's Hospital for Children at age 9 days. On examination, gangrenous tissue extruded through a necrotic scrotum (Fig 2). Fluctuant inflammation extended into the left flank. The penis was swollen, but the urethra appeared normal and the urinary stream was adequate. On visual inspection, the testicles appeared normal.

Laboratory studies showed a WBC count of 27,300/cu mm, with 63% neutrophils, 14% band forms, 20% lymphocytes, 3% monocytes, occasional Döhle bodies, and slight toxic granulations. The hemoglobin and BUN levels were normal. Results of urinalysis were normal. Blood culture was negative. *Escherichia coli* and group D streptococcus were cultured from the scrotum; *E coli* was also cultured from the abscess. The admitting diagnosis was gangrenous necrotic destruction of the scrotum and abscess of the abdominal wall. The patient was given methicillin sodium intramuscularly (IM) and kanamycin sulfate IM for seven days. Later the diagnosis was changed to Fournier's gangrene of the scrotum, with associated abdominal cellulitis. The scrotum was debrided, irrigated with hydrogen peroxide, and packed with iodoform gauze; the abscess in the flank was drained.

Regeneration of the scrotum was rapid (Fig 3). The child was discharged after seven days of hospitalization. At a follow-up examination, one testicle could not be felt while the other appeared normal by palpation.

Case 3.—At age 9 months, hot soup spilled on this child's perineum. Hexachlorophene and a combination of polymyxin B sulfate, bacitracin zinc, neomycin sulfate, and hydrocortisone (Cortisporin Ointment) were prescribed. Three weeks later vomiting developed, and the scrotum, perineum, and tip of the penis became swollen and discolored. The patient was admitted to a hospital, where he was treated with penicillin G potassium and kanamycin sulfate. Urinary fistulas developed in the perineum. A urinary tract infection developed, and ampicillin sodium was added to the treatment regimen. The patient was transferred to St Christopher's Hospital for Children. On admission he was chronically ill and cachectic. He had gangrene at the tip of the penis; necrosis of the scrotum, perineum, and penis; exposed testes; three to four fistulas in the perineum; anal stenosis; a healed inguinal incision; and a cystostomy tube (Fig 4).

Laboratory studies showed normal urinalysis findings, except for nine RBCs and four WBCs per high-power field and many

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Fig 1.—Case 1. Gangrene at base of scrotum and tip of penis.



Fig 3.—Case 2. Regeneration of scrotum.



Fig 2.—Case 2. Destruction of scrotum with extruding gangrenous tissue.



Fig 4.—Case 3. Destruction of perineum, gangrene at tip of penis, partial destruction of ventral side of penis, destruction of most of scrotal sacs, and exposure of testes.

bacteria. The total serum protein level was 4.5 mg/dl, and the albumin level was 1.9 g/dl. Levels for hemoglobin and serum sodium, potassium, calcium, and phosphorus as well as the CSF were normal. The WBC count and differential cell count were normal.

Citrobacter species, *Klebsiella*, and yeast were cultured from the scrotum and the glans penis. More than 10^5 colonies per milliliter of *Klebsiella* and *E coli* were grown from the urine specimen. The stool, blood, and CSF cultures were negative.

A cystogram showed a normal posterior urethra and distortion and destruction of the remaining urethra. Flow of contrast material near the perineum suggested extravasation.

The patient was treated with oral sulfisoxazole, given sitz baths, and placed on a Bradford frame. On the third day, a transverse colostomy was performed to relieve an intestinal obstruction secondary to a rectal stricture. Oral cephalexin monohydrate therapy was started on day 10. On day 12 there was a wound dehiscence and evisceration, which was closed surgically. Total parenteral nutrition was instituted along with kanamycin sulfate IM. The wounds of the perineum, scrotum, and penis continued to heal. A barium enema examination disclosed an inflammation involving the rectum and sigmoid colon, with a possible ileocolic fistula. Further surgical treatment was considered inadvisable until the nutritional status improved.

On day 34, at the time of discharge, the perineum had almost completely healed, and the baby had a functioning colostomy and a suprapubic tube. Treatment with sulfisoxazole and ferrous sulfate was continued at home. The child had several subsequent admissions that involved management of the following: revision of the colostomy to correct a prolapse, two-stage repair of a hypospadias, abdominoperineal pull-through with maintenance of a diverting colostomy, laparotomy for lysis of adhesions, and reconstruction of the penis. The testicles remained intact and appeared normal by palpation. At the age of 3 years, the child died at another hospital. Autopsy findings showed acute peritonitis, aspiration pneumonia, bilateral hydronephrosis, and hydroureters. The testicles were not examined.

COMMENT

The peak incidence of Fournier's syndrome is between ages of 20 and 50 years.[6,17] Though rare, the condition has occurred in females.[7,18] With two exceptions, authors allude to cases in children but offer little discussion.[5,6,9,12] Gibson[9] stated that cases in the first decade of life were usually in children younger than 3 years, with the majority in infants a few days to weeks of age. In two of our patients, the infection, which was identified at approximately nine and 17 days, may have started earlier.

The predisposing conditions that provide a portal of entry for pathogens that produce Fournier's syndrome include trauma, local or systemic infections, and structural abnormalities.[5-15,17,19-22] The portal of entry in case 1 was a recent diaper rash; in case 2, a recent circumcision; and in case 3, an open perineal wound from a hot scald burn. A review of the literature indicates that Fournier's syndrome is not a well-documented complication of a circumcision in the newborn.[23-30] On the other hand, beyond the newborn period, gangrene of the penis was reported in a 32-year-old man who had a circumcision for balanitis.[19]

A wide variety of Gram-positive organisms, enteric bacilli, and anaerobes have been identified as pathogens.[5-10,12-17,31,32] To these pathogens we add three new isolates from our

cases: group D streptococcus, *Enterobacter clocae*, and the *Citrobacter* species.

Causative organisms spread into the subcutaneous tissue and produce an obliterative endarteritis in branches of the internal pudendal artery and superficial and deep external pudendal branches of the femoral artery.[6-8,10,11,16,33] This leads to ischemic necrosis and gangrene of the scrotum. The spermatic arteries are generally not affected, and this protects the testicles.[16]

In adults, the onset is usually with fever, prostration, pallor, nausea, vomiting, tachycardia, delirium, and an inflamed scrotum. Gangrene usually develops by the third day, but may be as early as 12 hours or as late as 30 days. There may be an extension of gangrene onto the penis. If gas-forming organisms are present, crepitation may be present in the scrotal area and extend onto the abdomen and perineum. Abscess formation may appear as the infection spreads under Scarpa's fascia onto the abdominal wall and occasionally to the flank, lumbar area, posterior thorax, axilla, and under Colles's fascia onto the perineum. On rare occasions, there may be involvement of the anus, rectum, and thighs. In some patients, gangrene may first develop along the shaft of the penis. Within five to ten days, there is a slough at the line of demarcation. Secondary hemorrhage may occur, and toxicity disappears unless there are complications. With a slough of the scrotum, the testicles are suspended by the spermatic cords and are visible down to the tunica vaginales. The testicles, epididymis, and tunica vaginales are almost always spared, except for rare instances of gangrenous involvement. The scrotum heals rapidly by cicatrix formation. Complications include metastatic abscesses, pulmonary embolus, purulent peritonitis, intercurrent infection, sepsis, or paralytic ileus. Deaths have been reported 36 hours to 33 days after the onset of the disease. Mortality rates have varied from 7% to 32%.[7-12]

The findings in our cases were similar to those reported in the literature except for the absence of toxicity and complications. In one patient (case 2), one testicle could not be palpated after healing. It could have been lost in the gangrene or undescended. One patient died (case 3) of complications, none of which was secondary to Fournier's syndrome. There is little room for a differential diagnosis when gangrene appears; however, before that one should consider torsion of the testicle or appendix testes, epididymitis, acute hydrocele, strangulated hernia, cellulitis, trauma, diabetic gangrene, periurethral phlegmon, pelvic phlebitis, and edema from renal, cardiac, or liver disease.[8,9,14]

Management includes culture for aerobic and anaerobic organisms and treatment with antibiotics based on findings from sensitivity studies, debridement, irrigation with Dakin's solution, topical antibiotics or local dressings with gadoment ointment, and general support. Multiple incisions with placement of drains and irrigation with hydrogen peroxide are necessary if crepitation is felt. While controversial, gas gangrene antitoxin and tetanus antitoxin should be given for clostridial infections.[8,11,14,15,32] Suprapubic cystostomy may be necessary.[15] While grafts were not used in our patients, they have proponents and opponents.[7-10,13-15,17,19,33] If the penis, urethra, or both are involved, reconstructive surgery may be necessary.[32]

It is surprising that this syndrome does not occur more often in normal male infants. A diaper rash or a recent circumcision, both of which are common, provided a portal of entry for the invasion of organisms. While the environment seems conducive for the development of Fournier's syndrome in infants, fortunately it is rare.

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Nonproprietary Names and Trademarks of Drugs

Ampicillin sodium—*Alpen-N, Amcill-S, Omnipen-N, Penbritin-S for Injection, Polycillin-N for Injection, Principen/N.*
Cephalexin monohydrate—*Keflex.*
Gentamicin sulfate—*Garamycin.*

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Oral Gentamicin Therapy in the Prevention of Neonatal Necrotizing Enterocolitis

A Controlled Double-Blind Trial

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• The value of prophylactic oral gentamicin sulfate therapy in the prevention of necrotizing enterocolitis (NEC) was evaluated in a group of 42 high-risk neonates over a four-month period in a randomized, double-blind controlled trial. Twenty babies in the treatment group received 2.5 mg/kg of gentamicin sulfate every six hours for one week after birth, and 22 babies received dextrose-and-water placebo in an equivalently small volume.

None of the 20 gentamicin-treated babies developed NEC. Four of the control babies did. Two of these babies died, and their diagnosis was pathologically confirmed. This difference in the incidence of NEC between the treatment and control groups was significant at the .05 level.

These results support the prophylactic use of orally given gentamicin for selected babies at high risk for NEC, particularly those born prematurely and those who have a history of perinatal asphyxia or umbilical artery catheterization or both. Continued surveillance for changes in antimicrobial sensitivity patterns is recommended.

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Neonatal necrotizing enterocolitis (NEC) is a syndrome seen especially in prematurely born infants and causes substantial morbidity and mortality.[1-4] The most commonly reported characteristics of this disease are bloody stools, abdominal distention, ileus, pneumatosis intestinalis, and intestinal perforation.[1-4] Prominent factors proposed for the etiology of NEC are perinatal asphyxia, hypotension, infection, milk feedings, and umbilical catheters.[1-4]

Subsequent to an increased incidence in NEC in our nursery, affecting more than 10% of premature infants during a three-month period, and because of a previous report by Egan and associates[5] noting the successful use of oral aminoglycoside antibiotic prophylaxis, we undertook a prospective, double-blind study to compare orally administered gentamicin sulfate with placebo in preventing NEC.

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SUBJECTS AND METHODS

All newborns weighing under 1,500 g, all babies of any weight who had an umbilical catheter, and all premature babies who had a history of fetal distress, postnatal asphyxia, or hypotension (defined as the need to use colloid solution to raise systolic blood pressure above 40 mm Hg) were considered at high risk for NEC and thus eligible for entry into the study. Placement into the treatment or placebo group was done through random assignment by blind card draw. The hospital pharmacy acted as the referee for treatment group assignment. Informed written consent was obtained from the mother of each patient. The treatment group received 2.5 mg/kg of gentamicin sulfate at a concentration of 2.5 mg/ml in 5% dextrose in water every six hours by mouth for seven days, starting immediately after birth. A similar volume of 5% dextrose in water was given to the control group according to the same dosage schedule. Forty-two consecutive high-risk patients were studied during the four-month period of the study.

Oral feedings were begun after resolution of any acute illness and 24 hours after removal of any umbilical catheter. The 5% dextrose solution was used as the initial feeding, followed by fresh breast milk, if available, or standard formula. Feeding was administered by nipple or by intragastric or intrajejeunal routes. Initial feedings were less than 5 ml/kg in the premature infants. All umbilical arterial catheters were uniformly placed at the L4-5 level.

The clinical diagnosis of neonatal NEC was based on the presence of bloody stools, abdominal distention, residual or regurgitated feedings, and radiological findings of pneumatosis intestinalis and bowel wall edema. If surgery was done or the baby died, pathological examination was confirmatory. In addition, there were babies who had NEC-like illnesses or enteropathies, characterized by guaiac-positive stools, intermittent abdominal distention, and residual feedings. All diagnoses were made by independent observers, namely neonatology fellows, prior to breaking the treatment code.

In each baby in whom NEC or NEC-like illness developed, the study wes terminated, feedings stopped, gastric decompression performed, intravenous antibiotic therapy started, and gentamicin administered orally. The code was not broken. Stool and blood cultures were obtained from all infants with NEC or NEC-like enteropathies.

RESULTS

Table 1 shows the incidence of NEC, the related mortality, and the incidence of NEC-like enteropathies. The four babies with definite NEC were premature; all were fed prior to the onset of the disease. The two babies who died were both small for gestational age, had a history of fetal distress, and were not acutely ill after birth until the onset of the disease on the second and third days of life, respectively. The third baby with NEC, a second twin, was born at 30 weeks' gestation, had perinatal asphyxia, placement of an umbilical artery catheter, and hyaline membrane disease. Neonatal necrotizing enterocolitis developed on day 13. The fourth baby was born at 33 weeks' gestation and had appropriate weight for gestation. This baby had hyaline membrane disease and an umbilical artery catheter; NEC was diagnosed on day 3. No baby outside of the study had NEC or NEC-like enteropathy during the four-month study period.

Table 1.—Results of Gentamicin Prophylaxis

	Gentamicin Prophylaxis (N = 20)	Control (N = 22)
Necrotizing enterocolitis	0	4*
NEC-related deaths	0	2
NEC-like enteropathies	1	5*

*$P < .05$ (χ^2).

A comparison of the treatment and control groups for those perinatal factors previously associated with NEC is presented in Table 2. There were no significant differences between the two groups found for these variables. Although average one- and five-minute Apgar scores did not differ statistically, there were, however, a greater number of five-minute Apgar scores below 7 in the treatment group. There was no difference in the incidence of systemic antibiotic usage prior to the onset of gastrointestinal signs or symptoms in the two groups.

Since the inception of routine oral gentamicin prophylaxis in our nursery 12 months ago, there has been a less than 1% incidence of NEC in the premature population. The one case occurred at 7 weeks of age in a baby with chronic pulmonary insufficiency.

COMMENT

The hypothesis that oral gentamicin administration to newborns at risk for NEC prevents this disease is supported by these data since there was a statistically significant difference in the occurrence of NEC between the two groups. The lack of definite NEC cases in the treatment group is similar to the results obtained by Egan et al with orally administered kanamycin sulfate.[5,6] Furthermore, there were no significant differences ($P > .05$) between groups in feeding patterns, placement of umbilical catheters or duration of catheterization, confirmed episodes of hypotension or hypoxia, and the incidence of hyaline membrane disease. This equal distribution of variables that have previously been associated with NEC allowed us to evaluate oral gentamicin therapy as a single factor.

Numerous authors have speculated on the role of bacterial colonization of the gut after birth and subsequent invasion of injured mucosa as important factors in the etiology of NEC.[1,2,7-9] We postulate that oral antibiotic administration reduces the colonization and multiplication of such

Table 2.—Comparison of Study and Control Groups

Characteristic	Gentamicin Prophylaxis (N = 20)	Control (N = 22)
Birth weight, g	1,733 (640-3,400)*	2,088 (780-4,400)*
Gestational age, wk	33.1 (26-40)*	34.2 (27-41)*
Apgar scores		
1 min	5.3 ± 2.8†	4.7 ± 2.4
5 min	6.6 ± 2.1	7.3 ± 2.0
Hypotension (systolic blood pressure < 40 mm Hg)	12	11
Hypoxia (arterial Po_2 < 40 mm Hg)	8	5
Initial feeding		
Day	3 (1-13)*	4 (1-11)*
Volume, ml/kg	5.2	5.5
Breast milk	9	10
Respiratory distress syndrome	9	11
Patent ductus arteriosus	7	5
Umbilical artery catheters	17	19
Duration 45 hr	(2 hr-6 days)	40 hr (1 hr-4 days)
Umbilical venous catheters	2	1
Duration, hr	4.5	6.0
Exchange transfusions	2	3

*Mean (range).
†Mean ± SD.

organisms in the neonatal bowel. Boyle et al[10] have recently shown a reduction in enteric colonization with coliforms while using orally administered kanamycin, and suggest that this provides partial protection from NEC. *Escherichia coli* and other Gram-negative bacteria are most commonly reported in this association.[1,2,8] There were no pathologic organisms consistently isolated from the stools of our patients with NEC or NEC-like illness. This experience is consistent with a previous report[11] that showed an inconsistent relationship between stool flora and the occurrence of NEC.

We specifically chose gentamicin in the present study not only for its limited absorption from the gastrointestinal tract,[12] but also because there were no gentamicin-resistant organisms identified during continued stool surveillance in our nurseries. The oral dosage used is routine in the treatment of neonatal NEC.

Of the four babies with NEC in our study, prematurity plus a history of severe fetal distress in two were the major risk factors. The presence of placental insufficiency may lead to "selective circulatory ischemia" as a defense against asphyxial damage.[13] In this process, blood is shunted away from the mesenteric vascular bed to maintain myocardial and CNS perfusion. It has been proposed that such diminished gastrointestinal perfusion may lead to decreased mucous production that allows bacterial invasion, then proliferation of gas-forming organisms within the bowel wall.[1] Book et al[14] have recently described another approach to prevention of NEC through the use of infection-control measures that interrupt fecal-oral spread of a transmissible agent. The benefit of such infection control measures provides further support to our hypothesis that antibacterial prophylactic techniques are important in preventing NEC.

It is interesting to note the differing incidence of NEC-like enteropathies between the two groups. Five infants in the control group, but only one in the treatment group, were affected. This group of signs and symptoms may represent a percursor or early stage of NEC, as previously discussed by Santulli et al[1] and Egan et al.[5] Whether these cases of NEC-like enteropathy would have been self-limited or benign is unknown. After the appearance of symptoms they were all treated by their physicians with a regimen of no feedings, intravenous alimentation, parenteral antibiotic administration, and oral gentamicin therapy.

The findings of this study support the prophylactic use of oral gentamicin therapy starting at birth in selected babies at high risk for NEC, particularly premature infants with a history of perinatal asphyxia or placement of an umbilical artery catheter. This practice is most advisable when there has been an increased incidence of NEC in that intensive care nursery. Continued surveillance for the emergence of gentamicin-resistant organisms should be done if such prophylaxis is used to identify any change in antibiotic sensitivity patterns.

Still at issue is the question of whether to use oral aminoglycoside prophylaxis after the first week of life in a baby who has an ongoing risk because of ischemic episodes. We believe that this aspect of preventive care needs further evaluation.

Nonproprietary Name and Trademark of Drug

Gentamicin sulfate—*Garamycin.*

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Oculoglandular Disease of Parinaud

A Manifestation of Cat-Scratch Disease

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• Among patients with cat-scratch disease, the oculoglandular form is the most common unusual manifestation. This condition, seen in 14 of 585 patients with the infection encountered in a private pediatric practice over a span of 23 years, belongs in the syndrome of the oculoglandular disease of Parinaud. Most of the 14 patients described were only mildly ill and had but little discomfort. All patients recovered without residuals. Diagnosis is based on four criteria: exposure to a cat, usually an immature one; the presence of a localized granuloma of the eye; the presence of preauricular lymphadenopathy; and a positive skin test to cat-scratch antigen of known potency. Several unusual features, never before described, of oculoglandular disease due to cat-scratch disease are submitted.

(*Am J Dis Child* 132:1195-1200, 1978)

Cat-scratch disease is probably the most common cause of single node lymphadenopathy seen in children and young adults, except those caused by obvious infections of the skin or upper respiratory tract. Usually, it is a mild disease; most cases probably are undiagnosed and almost certainly many persons who are affected do not seek medical care.

Oculoglandular involvement is the most common atypical manifestation of cat-scratch disease. As seen in Table 1, it has been encountered 14 times among 585 patients recognized by me and my colleagues in an office practice since 1955. This article summarizes the clinical pictures of these patients, several of whom had manifestations never before described.

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HISTORY

The oculoglandular cat-scratch disease syndrome was described by Henri Parinaud in 1889[1] (Fig 1). Previous to his description of three patients with oculoglandular disease, he described a supranuclear paralysis of upward movement of the eyes that also bears the designation of "Parinaud's syndrome." This has led to confusion in the medical literature and emphasizes the importance of referring to the eye condition related to cat-scratch disease as the "oculoglandular syndrome of Parinaud," rather than simply Parinaud's syndrome.

Parinaud's disjointed account of oculoglandular disease, entitled "Infectious Conjunctivitis Apparently Transmitted to Man by Animals," leaves one with the impression that his three patients may have had a severe manifestation of this form of cat-scratch disease. Despite many references implying otherwise, it is erroneous to conclude that he suspected cats or other small animals to be vectors of the disease that he described. Actually, his suspicions of animals as a source were aroused because one of his patients was a butcher; and another, a child, lived near an unsanitary slaughter house.

After Parinaud's account, numerous reports of granulomatous eye conditions, usually unilateral, with involved lymph nodes on the same side of the face or neck were reported. These reports through 1965 were summarized by Duke-Elder[2(pp379-382)] and Cassady and Culbertson.[3] Many authors concluded that their patient's disease was due to tuberculosis, tularemia, syphilis, or lymphogranuloma venereum.

In 1913, Verhoeff[4] demonstrated the presence of leptothrix in sections of material taken from cases of Parinaud's conjunctivitis. This organism was believed to be the cause of the condition by many observers, especially after the publication of the extensive paper by Henry[5] in 1952. Twelve of her patients were exposed to cats, four slept with them, but none had cat-scratch skin tests. It is now believed that leptothrix is a saprophyte, and it certainly is not the cause of oculoglandular disease of Parinaud associated with cat-scratch disease.

The first conclusive evidence that the syndrome may be caused by cat-scratch disease was given by Presme and Marchand,[6] who described oculoglandular disease in a 6-year-old child who had intimate exposure to a cat and a positive skin test for cat-scratch disease. There quickly followed reports of other patients by de Lavergne et al,[7] and Clement et al.[8] In this country, Daniels and MacMurray[9] reported two cases, verified by positive cat-scratch skin test. Cassady and Culbertson[3] described four patients with typical involvement of the eye and lymph nodes who had positive skin tests for cat-scratch disease.

Table 1.—Atypical Manifestations Seen Among 585 Patients With Cat-Scratch Disease

Manifestations	No.
Oculoglandular disease	14
Encephalitis	2
Osteolytic lesion	1
Thrombocytopenia	1
Erythema nodosum	1

PATIENTS AND METHODS

Each of the 14 patients with oculoglandular manifestation of cat-scratch disease described in this article were seen at least twice by me in private practice. The criteria used for diagnosis were lymphadenopathy, usually single but sometimes regional, intimate exposure to a cat, usually an immature one, the presence of an inoculation site on eye structures, and a positive skin test to cat-scratch antigen of known potency. Elimination of all other possible eye disease, which could involve prolonged and extensive studies, was considered unnecessary. All patients, however, had negative reactions to a standard test for tuberculosis. When discharge was absent, cultures were not taken from the eye, nor were viral studies obtained.

The patients (Table 2), all white, varied in age from 5 through 15 years of age. There were eight boys and six girls in the group. As with cat-scratch disease in general, the oculoglandular manifestations may be considered primarily a disease of childhood and adolescence.

REPORT OF CASES

CASE 1.—A 14-year-old boy who played almost daily with a neighbor's kitten complained of swelling in front of his left ear of one week's duration. The preauricular lymph node measured 2 cm in diameter and was slighty tender. Examination of the eye was negative except for a conjunctival granuloma measuring 3 to 4 mm near the upper fornix on the left (Fig 2). There was no erythema of the conjunctivae except at the well-demarked, almost hidden site, and there was no exudate. A skin test for tuberculosis was negative, and a cat-scratch skin test was positive at 48 hours. This youth was seen each day after school for more than three weeks. His general health remained good and he repeatedly denied eye discomfort although the involved lymph node remained tender. Both the granuloma and lymph node regressed about 50% in size in one month. After two months the lesions disappeared.

This boy had no discomfort other than lymph node tenderness and no constitutional symptoms. He is the most usual type of patient with the oculoglandular form of cat-scratch disease. He missed no time from school and medical advice had been sought because of preauricular lymphadenopathy only. He required no treatment.



Fig 1.—Henri Parinaud (1844-1905), a celebrated soldier in Franco-German War and distinguished Paris ophthalmologist, combined practice with research and conducted gratuitous eye clinic that attracted students from around world. Two important syndromes involving eye bear his name.

CASE 2.—Sixteen days after having a romp with his grandmother's cat, a 5-year-old boy had mild erythema of his right eye with preauricular lymphadenopathy on the same side. When seen five days later, there was a nodule on the bulbar conjunctiva with slight surrounding erythema (Fig 3). A culture of the eye was negative and blood leukocyte count was normal. A cat-scratch skin test was positive at 48 hours. Two weeks later, the inoculation nodule was still present and the lymph node had become fluctuant (Fig 4). Two and one-half milliliters of thick, blood-tinged pus was

Table 2.—Clinical Features of 14 Patients With Oculoglandular Disease of Parinaud Caused by Cat-Scratch Disease

Patient/Age, yr/Sex	Inoculation Site	Nodal Involvement	Fate of Node	Fever	Cat Exposure
1/14/M	Palpebral sclera upper conjunctiva	Preauricular	Regressed	None	Intimate, kitten next door
2/5/M	Ocular conjunctiva	Preauricular	Suppurated	None	Intimate, grandmother's cat, age unknown
3/14/M	Upper eyelid	Preauricular, 2 upper cervical	Regressed	None	Intimate, male, 2 kittens
4/15/F	Upper conjunctiva	Preauricular	Regressed	None	Sleeps with cat, plays with kittens
5/7/F	Cul-de-sac, lateral	Preauricular, 1 upper cervical	Regressed	None	Owns kitten
6/12/M	Double upper conjunctiva and palm of left hand	Preauricular and axillary (double inoculation)	Regressed	Low grade	Owns kitten
7/13/F	Upper conjunctiva	Preauricular, 2 upper cervical	Regressed	Low grade	Owns two cats
8/6/F	Lower conjunctiva	Preauricular, 2 upper cervical	Regressed	None	Owns kitten
9/8/M	Upper conjunctiva	Preauricular	Regressed	None	Owns 3-year-old cat
10/10/F	Lower fornix	Preauricular, 1 upper cervical	Regressed	None	Kittens next door
11/10/F	Lower conjunctiva	Preauricular	Regressed	None	Owns 3-month-old kitten
12/7/M	Upper conjunctiva	Preauricular	Regressed	None	Owns cat and kitten
13/7/M	Upper conjunctiva	Preauricular	Regressed	None	Owns cat and 4 kittens
14/7/M	Lower conjunctiva	Preauricular, 1 upper cervical	Regressed	None	Owns 2 cats and 1 kitten

aspirated from the lymph node. Nine days later, the lymph node was again fluctuant and 1.5 ml of pus was aspirated. Both specimens were negative on culture for bacteria. No fever was detected at home or on six office visits. He had pain for a few days shortly after he was first seen, but the condition was not incapacitating. All traces of eye infection were absent three months later.

This is probably the first patient described as having an inoculation site on the ocular conjunctiva. Perhaps, there was a minute break in the conjunctiva at this location allowing the causative agent to enter at this unusual site. In this series, there are two patients whose lymphadenopathy progressed to suppuration, and the severity of this patient's disease, in contrast to case 1, is unusal.

CASE 3.—A 14-year-old adolescent boy played with two "half grown" cats at a relative's home several days before the appearance of a red papule on the cutaneous surface of his upper eyelid. In several more days, this lesion became crusted. It remained only 3 to 5 mm in size. After three more days, it became an asymptomatic papule. Four or five days after discovering the papule on the lid, the preauricular lymph node on the same side became enlarged. Two physicians were consulted and two antibiotics were prescribed. He felt well and at no time was fever recognized. When seen by me, three weeks after onset, the papule on the eyelid was still present (Fig 5) and his preauricular node measured 1.5 cm, and the larger of two upper cervical nodes measured 3.5 cm. A cat-scratch skin test was positive. No treatment was given. At three subsequent examinations, regression of the nodes was apparent but five weeks after onset the inoculation site on the lid could be easily identified.

A granulomatous lesion of the conjunctivae is the usual inoculation site in this syndrome, but one can not exclude the skin of an eyelid as being part of the eye and this patient is included in the series as a most unusual one because of the inoculation site.

CASE 4.—A 15-year-old boy had a tender, swollen lump in front of his ear for five days. There was no fever, toothache, or earache. He had slept with a cat for three months. A preauricular node measured 1 cm in diameter. There was also moderate redness of the right upper eyelid. Two days later, the lymph node was moderately tender and became larger but he had no fever and felt well. There was a small red area with central ulceration of the conjunctiva of the upper lid. A cat-scratch skin test applied earlier was negative. Fourteen days after the onset of the illness, the lymph node was even larger, measuring 2×2.5 cm. There was now a granuloma of the right upper eyelid consistent with Parinaud's syndrome. A cat-scratch skin test was positive three days later, by which time both the enlarged lymph node and eyelid granuloma were regressing in size.

The initially negative test for cat-scratch disease has been observed in several additional patients with cat-scratch disease. They had negative skin tests during the first week of illness but positive ones later using the same or different antigens.

CASE 5.—A 7-year-old girl had owned a cat until shortly before her illness. She also played with cats in the neighborhood. Because of an unusual conjunctivitis with preauricular lymphadenopathy, she was admitted to a hospital by an ophthalmologist. When seen by me the next day, a raised area about 3 mm in diameter with slight surrounding erythema was seen in the inferior conjunctival cul de sac of the left eye (Fig 6). A preauricular lymph node on the same side measured 2.5 cm in diameter. Forty-eight hours later, a tuberculin test was negative and a cat-scratch skin test was strongly positive. Two upper cervical lymph nodes on the left side had become palpable and the preauricular node was increasingly tender. Bacterial culture from the eye was negative. Seven days later, the preauricular node measured 1.5 cm and the eye seemed normal. During the illness, she was ambulatory and no drugs were given.

This was the only patient in the series to be hospitalized. This provided observation of vital signs. Despite the



Fig 2.—Case 1. Inoculation site of cat-scratch disease on lower lid of eye showing in profile granulomatous nature of lesion.



Fig 3.—Case 2. Rare inoculation site on bulbar conjunctiva represented by white papule.

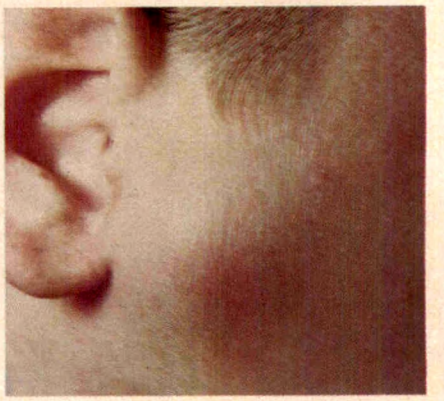


Fig 4.—Case 2. Preauricular lymphadenopathy early in course of disease.



Fig 5.—Case 3. Inoculation site, upper eyelid.

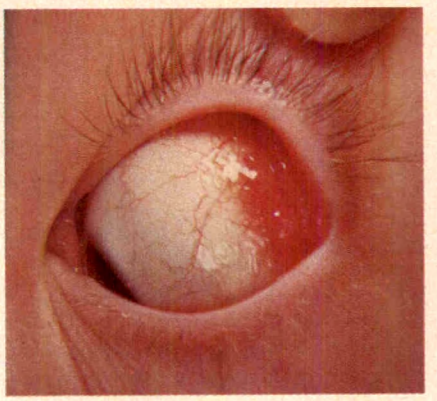


Fig 6.—Case 5. Inoculation site at fornix, an easily missed lesion.

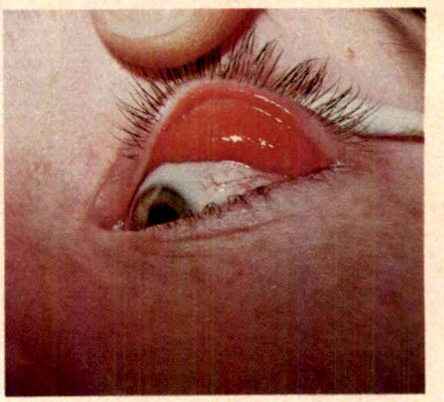


Fig 7.—Case 7. Inoculation site upper lid, early in course of disease.

fact that she had relatively severe manifestations, involving three lymph nodes, no temperature greater than 37.8 °C was recorded. She was the only patient with an inoculation site in the cul de sac of an eye.

Case 6.—Swelling of the preauricular lymph node on the right was noted about ten days before this 12-year-old boy was examined. No eye signs had been noted and he had experienced no pain. Three days after the facial swelling was apparent, a tumor in the left axilla that was slightly tender was noted. A granulomatous area on the lower right palpebral conjunctiva was seen and the preauricular node on the same side measured 2 × 2 cm. In the palm of the left hand, there was a papule that had been present before the axillary swelling. It measured several millimeters in diameter. This lesion was compatible with an inoculation site of cat-scratch disease. The left axillary node measured 2.5 cm in diameter and was moderately tender to pressure. The patient was never acutely ill and had no temperature greater than 37.8 °C. Abnormal physical signs disappeared after several weeks.

This boy was inoculated by the as yet undiscovered agent causing cat-scratch disease in the hand and in the eye at about the same time; a very unusual occurrence.

Case 7.—A 13-year-old girl noted left preauricular swelling about three to four weeks before being examined. Two weeks later, her left eye became hyperemic and, for one week, pus was noted in the eye, causing the eyelids to be "stuck together" one morning. She had received penicillin V and cloxacillin for four days prior to my first examination. Culture from the eye showed coagulase-negative staphylococci and corynebacterium. The involved preauricular lymph node measured 3 cm in diameter and there were two small upper cervical lymph nodes. She owned two cats aged 10 months. An ophthalmologist readily identified a granulation 4 mm in diameter on the upper lid near the lateral canthus (Fig 7), which was typical of cat-scratch disease of the eye. A skin test for cat-scratch disease was positive at 48 hours. Antibiotics were discontinued. On follow-up examination, one, three, and six weeks after her initial visit, the nodes were observed to regress, the preauricular node measuring only 1 cm at the last visit. The granuloma had become a 4-mm area of erythema on the last examination.

Of the 14 patients in this series, only this one had a purulent discharge from the eye. We suspect this to be a superimposed infection. Purulent conjunctivitis in childhood is common, but preauricular lymphadenopathy rarely accompanies such infections. The other seven patients involved in this report had no unusual features that require a detailed description.

CAT-SCRATCH DISEASE

The natural course of cat-scratch disease previously described by me[10]

and others[11-13] consists of an inoculation by an unidentified infectious agent, followed in about one week by the appearance of a maculopapular lesion measuring less than 1 cm in diameter. Some five to ten days later, lymphadenopathy appears in the drainage field of the inoculation site. The time between inoculation and appearance of a papule varies from a few days to as long as three weeks. The time between inoculation and lymph node enlargement varies from a few days to eight weeks.[12] Constitutional symptoms vary widely but usually are not incapacitating. Since it is our opinion that cat-scratch disease usually is a mild childhood infection and often overlooked, wide variation in recognition of manifestations is not surprising.

Inoculation Site

The most neglected feature in the diagnosis of cat-scratch disease is the identification of the inoculation site. In our series of 500 patients, only 5% failed to show a lesion at the place of inoculation and most of these had experienced the disease for more than three weeks before our first examination.

In the oculoglandular form of cat-scratch disease, the inoculation site presents typically as a granulomatous area on the conjunctiva. It is often polypoid in configuration, measuring about 0.5 to 2 cm in diameter and has an irregular border with little surrounding erythema. As the granuloma ages, it may enlarge and small whitish, yellowish, or grayish areas of necrosis may appear. Leptothrix, once thought to be the cause of granulomatous oculoglandular disease, has been demonstrated in necrotic areas. Pathogenic organisms are absent and secondary infection is unusual. Nearly always the inoculation occurs on the palpebral conjunctiva, as it did in 12 of our 14 patients. The inoculation sites were as follows: seven on the conjunctiva of the upper lid; four on the lower lid; one on the lateral conjunctival cul de sac; one on the skin of upper eyelid; and one on the bulbar conjunctiva. Involvement of the conjunctiva of both the upper and lower lids was seen in only one patient where the inoculation was in the cul de sac. The granulomatous tissue usually is not tender and if an exudate is present, it is sparse and mucoid in character. The site can be identified for several weeks, sometimes even for months, and it resolves without scarring. I could not relate the degree of lymph node involvement to the size of the lesion at the inoculation site.

Sim[14] said after study of sections of these granulomatous lesions, "There is nothing specific about these histological appearances as they could occur in any chronic inflammation."

Lymphadenopathy

Lymph node enlargement is essential for the diagnosis of cat-scratch disease. Usually only one node is enlarged. When bilateral enlarged lymph nodes are seen, as occurred in five of our 500 patients with the disease, there are two sites of inoculation or else an inoculation is near the midline of the body. I doubt that generalized lymphadenopathy occurs in the course of cat-scratch disease. The lymph nodes may vary widely in size and in degree of tenderness. They regressed over a period of weeks to months in about 85% of our series of 500 patients; the others became fluctuant and were drained of sterile pus, usually by aspiration.

Of these 14 patients with oculoglandular disease, seven had single preauricular node involvement and seven had cervical node involvement along with preauricular involvement. Only one patient had a suppurant lymph node. This was aspirated on two occasions (case 2). One patient required codeine because of pain in a preauricular node and the others either had no pain to moderate pain and tenderness of the involved nodes.

One of our patients (case 6) had typical cat-scratch disease involving an axillary lymph node with an inoculation site on the hand of the same side accompanied by oculoglandular disease, with an inoculation site on the upper palpebral conjunctiva. Such double involvement has never been described previously in Parinaud's syndrome caused by cat-scratch disease. Patient 3 is the only one of the group with an inoculation on the skin of an eyelid, and I believe that this site of inoculation has not been previously described.

We have seen patients with cat-scratch disease whose inoculation sites have been on the face, brow, and ear, and some of these have had preauricular lymphadenopathy. It should be emphasized that these patients do not have oculoglandular disease of Parinaud.

Cat Exposure

Among our 500 patients with cat-scratch disease, all except four had a history of exposure to cats. It is my belief that this animal is the only vector of the disease and in those few incidences in which a history of exposure cannot be elicited, the patient has been inoculated by some object or animal that was in contact with a feline. As has been noted by many authors, immature cats are more likely to transmit the agent than are mature ones. It seems logical to assume that the agent that causes the disease is harbored in the mouth of the animal and is transmitted to the human from cat by tongue, claw, or fur. In the case of oculoglandular disease, the agent is probably carried by a hand, which has recently touched a cat, to the eye. The agent might possibly enter the eye directly from the mouth of the cat, but this seems unlikely since cats do not cough or sneeze, although they do exhale bacteria and they spit.

Skin Test

The skin test for cat-scratch disease is a crude substance made from the pus aspirated from a fluctuant node of a patient with the disease. If the test is applied more than a week after the enlargement of the involved node and from material of known potency, all patients should have a positive test as did all 14 patients of this series. Of our 500 patients with cat-scratch disease, only seven had negative tests and were probably tested too early in the course of their disease. There may be occasional false-positive reactions, but I believe many such persons have had inapparent infection in childhood.

Diagnosis

Usually, a patient with the oculoglandular syndrome of Parinaud caused by cat-scratch disease will present with preauricular lymphadenopathy and not an eye lesion. An inoculation site should be found. This is not always easy, but with repeated examination and sometimes with the aid of special illumination and magnification in the office of an ophthalmologist, every patient should show a lesion consistent with the diagnosis. Finally, a cat-scratch skin test should be performed if possible. Transmission of disease by use of the cat-scratch skin test, which has been used since 1946 on thousands of patients, has not been described.

Diseases mentioned in the literature that might be confused with oculoglandular disease caused by cat-scratch disease are actually so dissimilar that little space should be given to their consideration. Duke-Elder describes syphilis,[2(pp236-243)] tuberculosis,[2(pp216-226)] lymphogranuloma venereum,[2(pp303-307)] and tularemia[2(pp204-209)] involving the eye. All of these diseases are usually much more severe than disease of the eye associated with cat-scratch disease; deep tissues are usually involved with tuberculosis and syphilis; there is much pus with lymphogranuloma venereum; history alone will usually give the clue in tularemia since 90% of patients with this condition have had intimate exposure to a rabbit; and moreover, a patient with tularemia is usually actuely ill with fever and ulceration of the eye occurs early and to a severe degree.[15]

The lack of discharge, either mucoid or purulent, among this group is striking. All of the patients were children or youths and one would not expect cleanliness and avoidance of eye contact to be characteristic of the group. Only one of the patients (case 5) had a purulent discharge and we suspect this was due to secondary infection. The eye reaction to cat-scratch infection alone would probably rule out the primary bacterial disease due to most any other agent.

The reason that preauricular involvement is always present in recognized cases remains a mystery. One sees bacterial and viral infections of innumerable types involving the eyes of humans when no nodal involvement is seen. As elsewhere in the body, invasion by the causative agent of cat-scratch disease provokes nodal response in a most provocative consistency. Perhaps, invasion of the eye by the agent that causes cat-scratch disease is more common than is recognized and only those patients who respond with lymphadenopathy are recognized.

The lack of fever among the patients is striking. Although it is true that temperatures were not checked at the homes of all the children in this series, inquiry was made of the parents concerning suspected fever and temperatures were taken on office visits. Although cat-scratch disease may be responsible for high fever, usually lasting only a few days, none of these children with oculoglandular disease had a recorded temperature greater than 37.8 °C.

TREATMENT

In the treatment of cat-scratch disease, controlled studies have never been made, to my knowledge. It is the impression of those who have treated large numbers of patients that antibiotics, including penicillin in all its forms, chloramphenicol, tetracycline, erythromycin, the cephalosporins, as well as the sulfonamides, do not reverse nodal enlargement and the ultimate suppuration that affects about 15% (our series) of recognized cases. Some of our referred patients had received three antibiotics, occasionally two simultaneously, by vein, as involved nodes became larger and larger and finally required drainage. The care of the eye in the oculoglandular type of cat-scratch disease should be only symptomatic unless secondary infection occurs, as it did in only one of these 14 patients. In this circumstance, local antibiotics in the form of drops or ointment probably are justified. The local use of anesthetics for eye pain was not considered necessary in this series; however, aspirin for several patients and codeine for one was prescribed for discomfort of the involved lymph nodes.

As with cat-scratch disease elsewhere, a suppurative lymph node should be aspirated with an 18-gauge or 19-gauge needle using local anesthesia. This is preferable to incision, which might promote a sinus formation. More than one aspiration, as occurred in case 2, may be required.

Surgical removal of granulomatous lesions involving the conjunctiva has been recommended as a means of shortening the course of the disease. When cat-scratch disease is the cause of the pathological process, this is not only unnecessary but is condemned.

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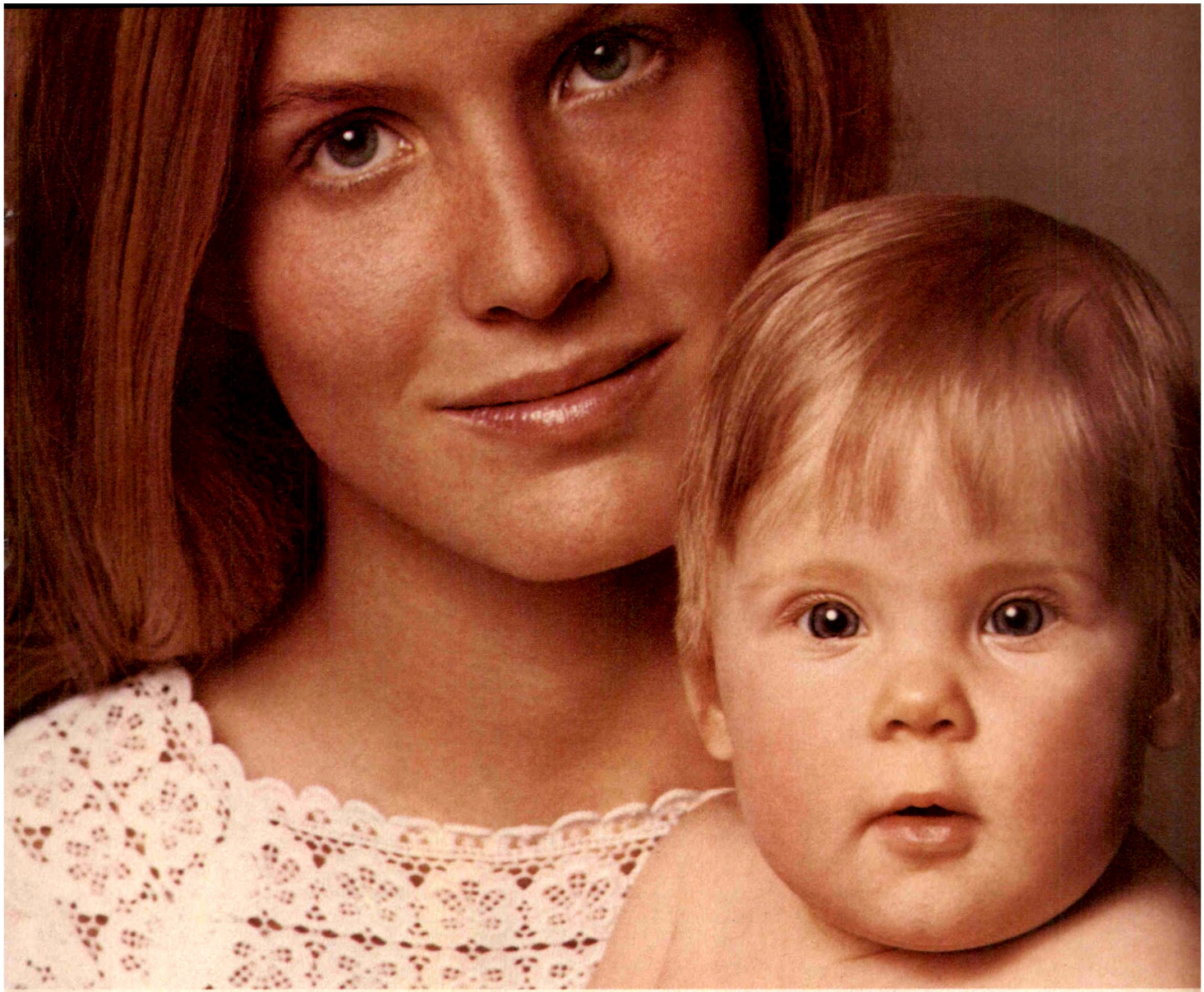
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[1] Material presented at March 23, 1977, symposium, Infant Nutrition: A Foundation for Lasting Health?



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Severe Infiltration of the Kidneys With Ultrasonic Abnormalities in Acute Lymphoblastic Leukemia

Ten Suan Goh, MB, BS, FRCP(C); Garry W. LeQuesne, MB, BS, MRACR; Kwan Yuen Wong, MB, BS

• **A 3-year-old boy with acute lymphoblastic leukemia had enlarged kidneys with impairment of renal function and hypertension as the presenting features of relapse. Ultrasound demonstrated multiple nodular areas of echolucency within enlarged kidneys that reverted to normal when the patient was in remission but then recurred during relapse. This noninvasive procedure may be useful in patients with acute lymphoblastic leukemia to determine the incidence and prognostic significance of renal involvement at the time of diagnosis, and to follow the course of those who have demonstrable changes.**

(*Am J Dis Child* 132:1204-1205, 1978)

Renal insufficiency in acute lymphoblastic leukemia is usually due to uric acid nephropathy. Leukemic infiltration of the kidneys is suspected when an elevation of the blood pressure is observed, although this is a rare complication.[1] The kidneys may or may not be palpably enlarged, and renal function is usually not severely disturbed.[2] Radiologic studies generally show enlargement of the kidneys with elongation and stretching of the renal pelves, infundibula, and calyces, which may simulate the appearance of polycystic disease.[3] Biopsy of the kidney for confirmation of the abnormality is usually not attempted because of an associated thrombocytopenia. Thus, the actual incidence of leukemic infiltration of the kidneys in acute lymphoblastic leukemia is unknown. We are reporting here the results of studies in a child with acute lymphoblastic leukemia who had considerable enlargement of his kidneys with impairment of renal function and ultrasonic changes in the kidneys as the presenting features of relapse.

REPORT OF A CASE

This 3-year-old boy with acute lymphoblastic leukemia had anemia, easy bruising, and hepatosplenomegaly. Blood pressure was 80/50 mm Hg. Serum uric acid level was 5.0 mg/dl; creatinine level, 0.7 mg/dl; and BUN level 14 mg/dl. He responded well to treatment with prednisone and vincristine sulfate, and remission was achieved after four weeks. He then received prophylactic treatment to the CNS in the form of whole brain irradiation with 2,400 rads and five doses of methotrexate intrathecally over a two-week period. Maintenance drugs were mercaptopurine and methotrexate.

Sixteen months after diagnosis, on a routine clinic visit, he was found to be hypertensive: blood pressure was 120 to 140/90 to 110 mm Hg. Both kidneys were markedly enlarged. Hemoglobin level was 11.0 gm/dl; white blood cell count was 5,400/cu mm, with 66% neutrophils, 17% lymphocytes, 5% eosinophils, and 12% monocytes. Platelets were quantitatively normal on the smear. The BUN level was 21 mg/dl; serum creatinine level, 1.2 mg/dl; and uric acid level, 6.0 mg/dl. Urinalysis showed a pH of 6.0, specific gravity of 1.012, albumin of 1+. On a centrifuged urine specimen there were three to four RBCs per high power field. Urine culture was negative for bacteria.

The excretory urogram demonstrated poor visualization of the kidneys; however, both kidneys were enlarged and the calyces were stretched and poorly filled. The collecting systems were not dilated and there was no evidence of obstruction.

The bone marrow was 75% replaced with lymphoblasts. A specimen of urine examined after cytocentrifugation disclosed the presence of blast cells. During the period of laboratory evaluation, there was progression of renal impairment: BUN level increased to 33 mg/dl and serum creatinine concentration to 2.2 mg/dl. He was treated with prednisone and vincristine. Within five days, his blood pressure returned to normal and the kidneys were no longer palpable. He was in remission after six

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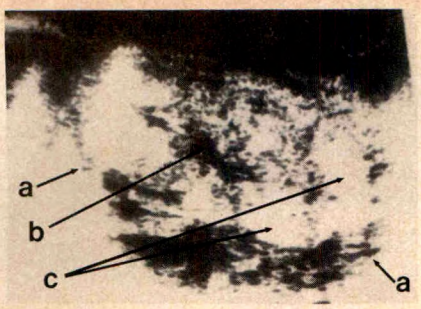


Fig 1.—Ultrasonic appearance of right kidney at time of presentation: a, renal outline; b, echoes arising from normal structures in renal sinus; c, nodular areas of echolucency separated by strands of compressed renal tissue showing increased echogenicity.

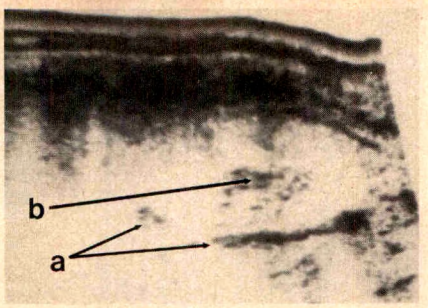


Fig 2.—After six weeks of treatment, appearance of renal parenchyma is now normal: a, renal outline; b, echoes arising from normal structures in renal sinus.

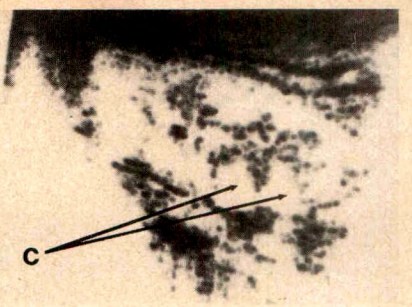


Fig 3.—Second relapse four months later. Ultrasound shows recurrence of nodular pattern (c) in renal parenchyma, although less marked than previously.

weeks of chemotherapy and was maintained with cyclophosphamide. His remission lasted only four months, at which time his bone marrow contained many blast forms, and he was treated with prednisone, vincristine, asparaginase, and doxorubicin hydrochloride (Adriamycin). During this period he became hypertensive again. He had a transient partial response only and died of progression of his leukemia. Autopsy was not done.

ULTRASONIC FINDINGS

Ultrasonic examination of the kidneys at the time of original recognition of the patient's hypertension confirmed the physical findings of enlarged kidneys. In addition, the renal outlines were nodular, and there were multiple areas of relative echolucency up to 3 cm in diameter within the kidneys (Fig 1).

Repeated ultrasonic examination after two weeks of chemotherapy showed a 4-cm reduction in renal length. The nodular pattern had disappeared although some areas of ultrasonic abnormality persisted within the kidneys. When the patient was in bone marrow remission, after six weeks of treatment, the echographic pattern of the kidneys was normal (Fig 2), as was the excretory urogram.

The kidneys were not clinically enlarged at the time when hypertension recurred during the second relapse. However, a 1-cm increase in renal length, together with a nodular pattern of the renal parenchyma, was again demonstrated with ultrasonic examination (Fig 3). The changes bore a striking resemblance to those seen in the original study, but were not as severe in degree. Further treatment was accompanied by loss of the nodular pattern, corresponding to the partial response in the bone marrow, but the appearance of the renal parenchyma did not return entirely to normal.

COMMENT

Marked enlargement of the kidneys with impairment of renal function and hypertension is extremely unusual as a sign of relapse in acute lymphoblastic leukemia.[4,5] The radiologic findings may not be specific. Transonic areas in the kidneys have been described in leukemia.[6] The improvement of the ultrasonic pattern of the kidneys corresponding with the clinical response to treatment of leukemia and its recurrence during relapse in our case suggests that the ultrasonic pattern was indicative of leukemic infiltration. Thus, it appears that ultrasonic examination of the kidneys may be a useful method for following the course of the disease in patients with acute lymphoblastic leukemia. Also, it is possible that the incidence of renal involvement and its prognostic significance could be determined by obtaining ultrasonic examinations at the time of diagnosis.

Cytocentrifugation has been shown to be useful in the diagnosis and management of meningeal leukemia.[7] The presence of blast cells in the urine in the absence of a bleeding diathesis suggests leukemic infiltration of the kidneys. However, the absence of blast cells in the urine in our patient during the subsequent relapse, despite the echographic changes, suggests that cytocentrifugation is helpful only if there is severe renal involvement.

The recommended treatment for leukemic infiltration of the kidneys is radiotherapy.[8,9] We have demonstrated in our case the rapid response of the renal leukemia to systemic chemotherapy, but the recurrence in our patient raises the question of whether chemotherapy alone is adequate. Further information on the incidence of renal leukemia is needed in order to evaluate its prognostic significance and the proper therapy.

This investigation was supported in part by general research support grant 5 S01 RR 05535-15 from the National Institutes of Health.

Nonproprietary Name and Trademark of Drug

Vincristine sulfate—*Oncovin*.

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Partial Exchange Transfusion in Sickle Cell Anemia

Use in Children With Serious Complications

Philip Lanzkowsky, MD, FRCP, DCH; Ashok Shende, MB, BS;
Gungor Karayalcin, MD; Young-Ju Kim, MD; Arturo J. Aballi, MD

• Seventeen children with sickle cell anemia received 40 partial exchange transfusions for serious complications of sickle cell anemia, and preoperatively to reduce the risk of anesthesia. Each patient received two partial exchange transfusions at 24-hour intervals and all patients tolerated the exchange transfusions well. The mean hematocrit level rose from 22.9% before the exchange transfusion to 40.6% at the end of the second exchange. The mean sickle hemoglobin level decreased from 93.8% before the exchange to 28.0% after the second exchange. Patients with acute lung syndrome had remarkable improvement in clinical symptoms and Pao_2 levels, and those with acute liver crisis had substantial reduction in serum bilirubin levels. All the other patients showed marked clinical improvement following the exchange transfusions.

(*Am J Dis Child* 132:1206-1208, 1978)

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Partial exchange transfusion in sickle cell anemia has been effectively utilized mainly in adult patients with symptomatic crises,[1,2] heart disease,[3] cerebrovascular crises,[4] and during pregnancy.[5,6] The purpose of this communication is to describe the usefulness of exchange transfusion in children who have serious complications from sickle cell anemia, and preoperatively to reduce the risk of anesthesia in children with sickle cell anemia.

SUBJECTS AND METHODS

From January 1976 through January 1978, seventeen children with sickle cell anemia received 40 partial exchange transfusions. Each patient received two partial exchange transfusions at an interval of 24 hours. Four of these children had sickle cell lung syndrome, three had liver crisis, two had acute papillary necrosis, two had pneumococcal meningitis, one had a painful crisis of five days' duration, and one had priapism; seven had exchange transfusions prior to surgery. Of those who received exchange transfusions preoperatively, one had an orthopedic procedure and six underwent cholecystectomy. Three of the patients who had preoperative exchange transfusions for cholecystectomy had previously had exchange transfusions, one for acute lung syndrome, one for acute liver crisis, and one for priapism. In addition to exchange transfusion, all patients received antibiotics, hydration, and oxygen therapy as required.

The exchange transfusion was carried out by transfusing 15 ml/kg of packed RBCs into the antecubital vein. Simultaneously, 20 ml/kg of whole blood was continuously removed by gravity from the opposite antecubital vein, using a disposable plastic, donor transfusion collecting unit. The exsanguinated blood was allowed to accumulate in a calibrated disposable, plastic bottle. Occasionally, other available veins were utilized for the transfusion and exsanguination. The rate of transfusion approximated the rate of blood removal. The entire procedure lasted from one to two hours and was repeated on the following day.

All the donors were negative for sickle hemoglobin and Australia antigen. The hemoglobin level, hematocrit value, quantitative hemoglobin S determination, serum bilirubin levels, liver functions, Pao_2, and clinical status were evaluated before and after each exchange transfusion.

RESULTS

All patients tolerated the partial exchange transfusion well. The mean hematocrit level rose from 22.9% (range, 17% to 28%) before the initial exchange transfusion to 40.6% (range, 31% to 52%) after the second exchange transfusion. The mean sickle hemoglobin level decreased from 93.8% (range,

Table 1.—Effect of Exchange Transfusion on Hematocrit (Hct) and Hemoglobin (Hgb) S Values in Children With Sickle Cell Disease With Serious Complications and Preoperatively

Diseases	N	Before Exchange		After First Exchange		After Second Exchange	
		Hct, %	Hgb S, %	Hct, %	Hbg S, %	Hct, %	Hgb S, %
Acute lung syndrome	4	20, 17, 23, 23	99, 98, 99, 96	29, 31, 26, 29	38, 41, 38, 54	39, 45, 38, 36	29, 21, 20, 30
Acute liver crisis	3	27, 27, 24	90, 95, 94	42, 36, 33	45, 37, 49	52, 39, 39	34, 25, 26
Acute papillary necrosis	2	22, 18	90, 97	34, 32	41, 40	41, 40	21, 24
Pneumococcal meningitis	2	26, 25	95, 82	32, 29	40, 39	37, 31	37, 32
Persistent painful crisis	1	19	94	37	46	41	30
Priapism	1	24	100	30	50	37	28
Preoperative	7	20, 23, 23, 25, 21, 27, 28	95, 93, 86, 59,* 68,* 60,* 92	39, 30, 33, 32, 35, 37, 33	38, 38, 40, 38, 48, 37,† 57	48, 42, 42, 40, 39, 43	28, 27, 33, 19, 29, 32
Range		17-28	82-100	26-42	37-57	31-52	20-37
Mean		22.9	93.8	32.7	43.0	40.6	28.0

*Patient had exchange transfusion previously. These values have been excluded from the determination of the range and mean.
†Patient received only one exchange transfusion.

Table 2.—Effect of Exchange Transfusion on Pao_2 (mm/Hg)* in Four Patients With Acute Lung Syndrome

	Before Exchange	After First Exchange	After Second Exchange
Values	40, 46, 48, 55	95, 90, 98, 93	100, 98, 99, 97
Mean	47.3	93.8	98.5

*In room air.

Table 3.—Effect of Exchange Transfusion on Serum Bilirubin Levels (mg/dl) in Acute Liver Crisis

	Before Exchange	After First Exchange	After Second Exchange
Total bilirubin			
Values	22, 27, 40	16, 17, 36	7, 14, 19
Mean	29.7	23.0	13.3
Unconjugated bilirubin			
Values	16, 17, 21	10, 11, 11	2, 7, 8
Mean	18.0	10.7	5.7

82% to 100%) before the initial exchange transfusion to 28.0% (range, 20% to 37%) after the second exchange transfusion. After the initial exchange transfusion, the range of hemoglobin S varied from 37% to 57%, with a mean of 43.0%; in 12 of these patients, the hemoglobin S value was 40% or more. Following the second exchange, however, all patients achieved a hemoglobin S level of less than 40% (Table 1). The reduction in hemoglobin S was due to a combination of the removal of hemoglobin S-containing cells as well as a dilution effect of the normal hemoglobin A cells accomplished by the exchange transfusion.

The patients with acute lung syndrome had remarkable improvement in their clinical symptoms and Pao_2 levels even after the first exchange transfusion (Table 2). In patients with acute liver crisis, the bilirubin levels were effectively reduced after the second exchange transfusion (Table 3). There was immediate cessation of hematuria in the patients with acute papillary necrosis following exchange transfusion, and the two patients with pneumococcal meningitis showed marked clinical improvement. The patient with refractory painful crisis for five days and the patient with priapism had immediate improvement and complete recovery following the procedure. The seven patients who had preoperative exchange transfusion had uneventful operative and postoperative courses.

COMMENT

The presence of sickle cells impairs microcirculation and plays an important role in the pathogenesis of vaso-occlusive complications in sickle cell anemia. Lessin et al,[7] using a rheometer, showed that the resistance of blood is reduced when a cell mixture contains less than 40% sickle cells in vitro compared to a higher percentage of sickle cells and that clinically vaso-occlusive crisis only occurs when the level of sickle hemoglobin exceeds 50%. A level of sickle hemoglobin of less than 40% is required in order to maintain normal microcirculation in patients with sickle cell disease and is especially important when severe complications are present. We were able to reduce the level of sickle hemoglobin to less than 40% in all patients by carrying out two partial exchange transfusions as described above. As the data indicate, a second exchange transfusion was required in order to consistently reduce the level of hemoglobin S to below 40% in all cases, whereas a single exchange transfusion achieved this level in only eight of 20 cases (40%).

Partial exchange transfusion removes irreversibly sickled RBCs, reduces the viscosity, and interrupts the cycle of vaso-occlusion, stasis, and venous thrombosis in the microcirculation. This results in better blood flow to the affected organ and helps to prevent or minimize tissue damage. In addition, exchange transfusions in refractory painful crises of sickle cell anemia assist in removing activated procoagulants and retard the formation of excessive thrombin and thereby help to restore normal microcirculation by decreasing relative

resistance. This might be important, as Leichtman and Brewer[8] have reported elevated plasma levels of fibrinopeptide A as evidence of the presence of intravascular coagulation during painful crises in sickle cell anemia. For these reasons, partial exchange transfusion is more effective than hydration, alkalinization, or blood transfusion in the treatment of serious complications of sickle cell disease. A simple transfusion is unable to reduce the level of sickle hemoglobin as effectively as the partial exchange transfusion without imposing volume overload and the risk of congestive heart failure. The chances of iron overload as a result of repeated blood transfusions are also minimized with the judicious use of exchange transfusion therapy.

Fulminant pneumococcal sepsis in sickle cell anemia patients carries a 29.4% mortality.[9] Exchange transfusion in patients with overwhelming infection may, in addition to providing better blood flow and oxygen delivery, also provide immunologic components at the site of infection, remove offending agents such as bacteria and endotoxins, and improve splenic function by improving the microcirculation.[10]

Priapism is a serious complication of sickle cell disease; it can occur at any age and may result in impotence. Surgical or conservative measures have not been found to be effective,[11] whereas exchange transfusion offers a successful alternative to therapy in this condition.

In sickle cell anemia, intralobular hepatic necrosis, infarction, abscess formation in infarcted areas of the liver, multifocal hepatic fibrosis, and postnecrotic cirrhosis have all been well described.[12-14] Obstruction of sinusoids by sickled RBCs plays a major role in the pathogenesis of these complications, and partial exchange transfusion is likely to reduce the severity of sequelae in hepatic crises.

In acute lung syndrome, Pao_2 values are often less than 75 mm Hg when patients are breathing room air.[15] Partial exchange transfusion is indicated if Pao_2 remains less than 75 mm Hg despite oxygen therapy, since at this level of Pao_2, damage as a result of widespread sickling is highly probable.

Spigelman and Warden[16] reported a 25% incidence of postoperative complications in 12 children who underwent 29 surgical procedures. Biliary tract disease was the most frequent indication for surgery in these patients. Preoperatively, many of them received either a regular transfusion or partial exchange transfusion. However, the amount of blood used for the transfusion or the exchange transfusion was inadequate to reduce the level of sickle hemoglobin below 40% in these patients. In view of the high postoperative complication rate and the absence of any perioperative complications in our seven patients, we suggest that partial exchange should be performed in patients with sickle cell disease preoperatively with the aim of reducing the level of sickle hemoglobin to below 40%. The need for adequate hydration and avoidance of oliguria, acidosis, and hyperosmolarity during the preoperative, intraoperative, and postoperative periods in these patients still remains important in their management.

Technically, the procedure of partial exchange transfusion is easy. It is mandatory that the donor's blood is negative for sickle hemoglobin. Although partial exchange transfusion should be used judiciously, our data suggest that it might be employed with benefit in serious complications of sickle cell anemia such as hepatic crisis, meningitis, acute lung syndrome, and priapism, and preoperatively where the potential for considerable and often irreversible tissue damage exists.

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Familial Mediterranean Fever

A Case Report

Edward A. Nichols, MD, Robert F. Reder, MD

• **A case of familial Mediterranean fever in a young girl presented typical diagnostic dilemmas. Although intermittent proteinuria was noted, a rectal biopsy specimen failed to demonstrate the presence of amyloidosis. Treatment consisted of supportive therapy and colchicine, to which she responded. In a cosmopolitan population, familial Mediterranean fever should be considered in the differential diagnosis of fever of unknown origin.**

(*Am J Dis Child* 132:1209-1210, 1978)

Familial Mediterranean fever is an hereditary disease having two major clinical manifestations: (1) acute, self-limited, paroxysmal, febrile attacks of peritonitis, pleuritis, or synovitis, and (2) amyloidosis.[1] Although this condition has its onset in the first or second decades of life, the diagnosis may not be entertained because it occurs primarily in people living in the Mediterranean Basin and it may mimic a host of more common illnesses. Indeed, many patients have undergone at least one abdominal operation for peritonitis before familial Mediterranean fever is diagnosed.

Recent immigration from the Middle East increases the likelihood that this relatively rare entity will be seen by the pediatrician. The following case report is presented to illustrate a typical clinical picture and to discuss treatment with colchicine.

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REPORT OF A CASE

The patient, a girl 8 years and 5 months old, was the 3,140-g product of a normal, full-term pregnancy and delivery. During her first year of life, routine physical findings were considered normal except for small capillary hemangiomas noted on her right breast and labia. At age 1 year, she was first brought to the office by her adoptive parents for routine health care. Over the course of the next two years, the child was seen for common childhood illnesses such as upper respiratory infections and otitis media.

At 3 years of age, she developed spiking fevers to 39 °C every third day for a period of ten weeks. On one occasion, the fever was associated with lethargy, vomiting, diarrhea, and an erythematous, maculopapular rash on the trunk and face. The patient was hospitalized for evaluation of the recurrent fevers. Physical findings were considered normal. Investigations for infectious and collagen-vascular etiologies were unrevealing. Fever was not recorded in the hospital, and the patient was discharged home. She was receiving 45 mg of aspirin four times per day.

In the intervening three months, the patient had weekly temperature elevations to 39.5 to 40.5 °C. A second hospitalization was prompted by a generalized seizure associated with pharyngitis and a temperature of 40.5 °C. Physical findings were normal except for pharyngitis and lethargy. Group A β-hemolytic streptococcus grew on throat culture. Evaluation of CSF, EEG, echoencephalogram, and brain scan were interpreted as within normal limits. The patient was treated with phenobarbital for febrile seizures and penicillin. Although the child became asymptomatic while in the hospital, she continued to have daily temperature elevations to 39 to 40 °C. Laboratory values determined during this hospitalization to elucidate the cause of the fevers included the following: hemoglobin, 12.0 g/dl; hematocrit, 34%; platelets, 380,000/cu mm; WBCs, 15,000/cu mm; monocytes, 13%; polymorphonuclear leukocytes, 67%; lymphocytes, 20%; ESR, 63 mm/hr; urinalysis, within normal limits; serum sodium, 138 mEq/liter; potassium, 4.9 mEq/liter; chloride, 101 mEq/liter; BUN, 8 mg/dl; total serum bilirubin, 0.1 mg/dl; SGOT, 14 IU; SGPT, 7 IU; alkaline phosphatase, 147 IU; total serum protein, 6.5 g/dl; albumin, 3.0 g/dl; α_1-globulin, 0.4 g/dl; α_2-globulin, 1.4 g/dl; β-globulin, 0.9 g/dl; γ-globulin, 1.0 g/dl; IgG, 800 mg/dl; IgM, 185 mg/dl; IgA, 150 mg/dl. Bacterial, mycobacterial, and viral cultures of the cerebrospinal fluid and blood showed no growth. A PPD skin test was negative, as was a blood smear for malaria. Febrile agglutinins, slide test for heterophil antibody of infectious mononucleosis, *Mycoplasma* agglutination, and toxoplasmosis titer tests were negative. No ova or parasites were present in the stool. A slit-lamp examination, antinuclear antibody, lupus erythematosus preparation, latex fixation test, VDRL, intravenous pyelogram, and gastrointestinal barium roentgenograms were normal. A bone marrow examination was "consistent with infection"; bacterial cultures showed no growth. After a hospi-

tal stay of eight days, she was dismissed on a regimen of phenobarbital, 25 mg by mouth three times per day, and aspirin, 45 mg by mouth every four hours. She was without fever at the time of discharge. A second bone marrow examination several weeks later was normal. Convalescent viral titers to influenza, parainfluenza, respiratory syncytial virus, adenovirus, *Mycoplasma*, and cytomegalovirus were not elevated significantly. Aspirin therapy was discontinued.

One month later, she developed fever to 38.9 °C, vomiting, and diarrhea associated with the acute onset of shoulder and ankle pain that lasted 24 hours. Symptoms remitted spontaneously.

Eight weeks later, episodes of fever and abdominal colic developed that lasted approximately three hours each. Physical findings two hours after one such attack were entirely normal. These "attacks" continued to occur intermittently over the next months. Between the episodes, she was entirely asymptomatic.

She was hospitalized again for observation because the intermittent abdominal pain and fevers continued. No fever, abdominal tenderness, or pain was recorded during this four-day admission. Urinalysis results were normal. The combination of recurrent fever, arthralgia, and a paroxysmal abdominal pain occurring in an otherwise asymptomatic child, however, suggested the possibility of familial Mediterranean fever. The adoption agency was able to supply information that the father was Algerian and mother French Huguenot in origin. A rectal biopsy specimen for amyloidosis was normal.

At 5½ years of age, the child was hospitalized for cosmetic removal of the breast hemangioma. A second rectal biopsy specimen was normal, and urine was negative for coproporphyrins and protein. After discharge, she continued to have monthly episodes of fever and abdominal pain. In addition, intermittent proteinuria was noted.

At 6 years of age, treatment was begun with 0.6 mg of colchicine given by mouth once per day. During the next nine months, she had two severe abdominal attacks, synovitis in the right index finger, and arthralgia in the left knee. Total urinary protein values, measured in a 24-hour urine specimen, were less than 0.02 g/24 hr. The dosage of colchicine was increased to 1.2 mg/day. A definite decrease in the intensity and frequency of the attacks occurred.

In the four months since the patient's eighth birthday (February 1978), she has had only one four-hour episode of fever and abdominal colic. She continues to receive 1.2 mg/day of colchicine. Testing for urinary protein by reagent strips at home has disclosed only occasional +1 to +2 values. The child is otherwise healthy, normal, and active.

COMMENT

Because no specific laboratory test exists to conclusively diagnose familial Mediterranean fever, this condition must be defined over a period of time, using the following clinical criteria: (1) brief, febrile, paroxysmal attacks of peritonitis, synovitis, pleuritis, and/or dermatitis; (2) ethnic origin from peoples of the Mediterranean Basin (especially Sephardic Jews); (3) autosomal recessive pattern of inheritance; (4) amyloidosis; and (5) absence of other, more common causes. Routine laboratory values are usually normal except for elevated erythrocyte sedimentation rate, decreased serum albumin, normal or increased γ-globulin and a large increase in fibrinogen, C-reactive protein, α_2-, β_2-, and α_2M-globulins, haptoglobins, and lipoproteins.[1] Our patient had acute, paroxysmal attacks of fever, joint pains, and abdominal pains for which no more usual cause could be discovered. Her ethnic origin was one in which familial Mediterranean fever was a possibility (ie, the Mediterranean region). Her erythrocyte sedimentation rate was elevated on at least one occasion; the serum albumin level was decreased, and α_2-globulin value increased. Finally, and of most concern, was the appearance of proteinuria. Two normal rectal biopsy specimens and the absence of noticeable urinary protein on a 24-hour urine collection indicated that amyloidosis was not present. The appearance of renal amyloidosis would have grave prognostic significance for while the acute attacks may be debilitating and demoralizing, they are not usually fatal. However, amyloidosis, the onset of which does not seem to be related to the acute attacks, is the major cause of mortality and shortened life span in this condition.[1] Continued lifelong surveillance for any deterioration of the renal status is needed in this patient.

Treatment directed toward the paroxysmal attacks usually consists of symptomatic therapy with analgesics once the attack is established and the use of colchicine in an attempt to prevent the attacks. Colchicine given on a chronic basis (0.6 to 1.2 mg by mouth every day) or acutely at the beginning of an attack (1.8 to 3.0 mg once by mouth),[2] seems to lessen the frequency and severity of the attacks. Colchicine, however, is not known to affect the course of amyloidosis. Because of the variability of the acute episodes in the untreated patient and because of the individual variation in response to therapy, response to treatment with colchicine cannot be employed as a diagnostic criterion of familial Mediterranean fever. Colchicine therapy is not without side effects. These include aneuploidy, azoospermia, nausea, vomiting, abdominal pain, diarrhea, agranulocytosis, aplastic anemia, peripheral neuritis, and hair loss.

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Radiological Case of the Month

Lionel W. Young, MD; Contributed by Julie S. Mitnick, MD; Joseph Yee, MD; Nancy B. Genieser, MD

Clinical History.—A 17-year-old boy had a two-day history of sore throat, low-grade fever, difficulty in swallowing, labored breathing, and excessive salivation. The oral cavity showed an excessive amount of saliva. The tonsils were enlarged but not exudative. The chest was clear to percussion and auscultation. A lateral roentgenographic view of the neck was obtained (Figure). Complete blood cell count showed 24,600 WBCs with 84% polymorphonuclear neutrophils 12% band forms, and 4% mononuclear cells. Hematocrit level was 46.5%. The remainder of the laboratory values were normal.

From the Department of Radiology, New York University School of Medicine, New York.

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Figure.



Denouement and Discussion

Figure.—The epiglottis is swollen and aryepiglottic folds are prominent.

Acute Epiglottitis in Older Children and Young Adults

Acute epiglottitis is a disease of infancy and early childhood that has been well described with regard to both its clinical and radiological findings.[1] This case of a 17-year-old patient emphasizes that identical symptoms and roentgenograms may occur in older children with *Haemophilus influenzae* epiglottitis, and that this entity is not as rare as was previously considered. Prompt diagnosis of severe airway obstruction is as critical in older children and adults as in the young patient with *H influenzae* epiglottitis.

Although this disease is severe and fulminant in infancy and early childhood, it has become increasingly evident that older children and adults may also be affected. In a recent study of acute epiglottitis in adults, only four of ten cases were diagnosed on initial presentation.[2] These patients frequently had a severe sore throat and difficulty breathing. Stridor, hoarseness, and increased oral secretions were common findings. Low-grade fever and leukocytosis were also found.

Although the most common causative organism in children is *H influenzae*, other organisms such as streptococci, staphylococci, and pneumococci have been implicated in the relatively older age groups. Hawkins and Miller[3] noted that the infection was usually more severe when *H influenzae* was the causative agent. In many cases, a bacterial isolate is not obtainable. The lateral roentgenogram of the soft tissues of the neck is helpful for affirming the diagnosis. This examination is best obtained in the upright position with the neck in mild hyperextension. The upright position also prevents posterior pharyngeal pooling of oral secretions that would further complicate airway obstruction.

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The Editors welcome contributions to "Picture of the Month" and "Radiological Case of the Month." Those who wish to contribute should send their manuscripts to Dr Gellis (Picture of the Month), Boston Floating Hospital, 20 Ash St, Boston, MA 02111, or Dr Young (Radiological Case of the Month), Department of Radiology, Children's Hospital of Pittsburgh, 125 DeSoto St, Pittsburgh, PA 15213. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.

Picture of the Month

Sydney S. Gellis, MD, Murray Feingold, MD
Contributed by F. Camarasa, MD; A. Gonzalez, MD; Santiago Garcia-Tornel, MD



Fig 1.

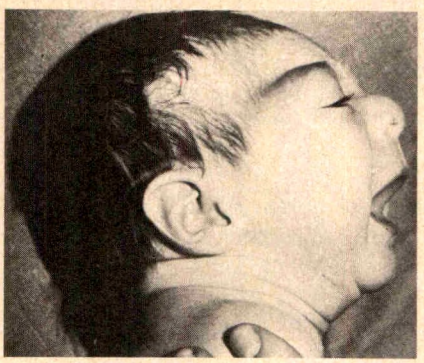


Fig 2.

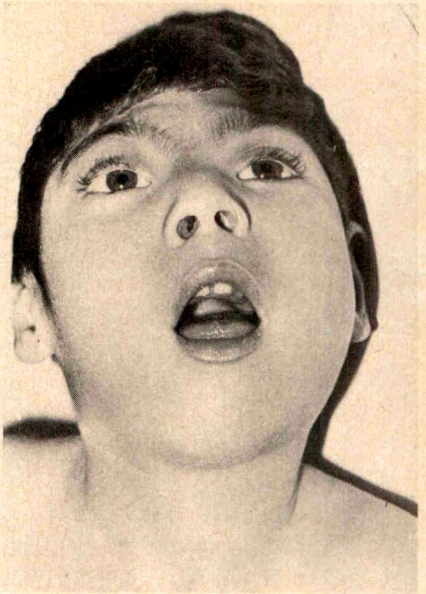


Fig 3.

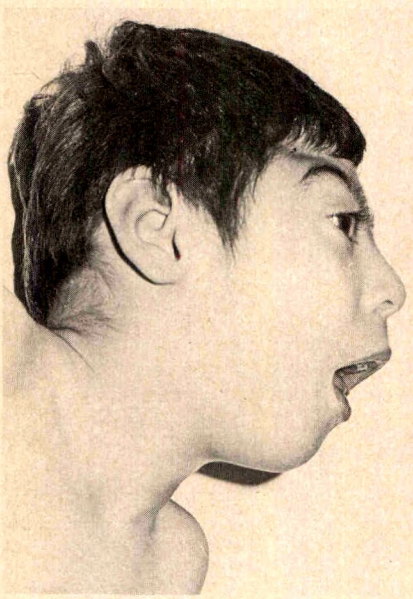


Fig 4.

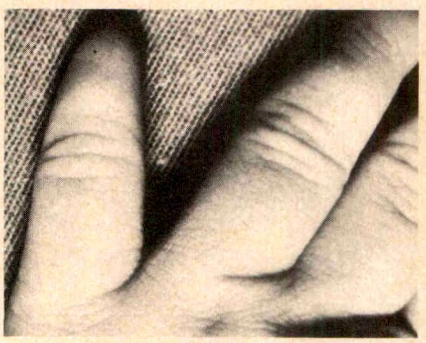


Fig 5.

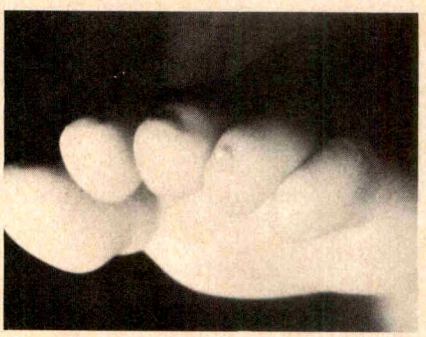


Fig 6.

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Denouement and Discussion

Coffin-Siris Syndrome

Fig 1.—Coarse facial features with microcephaly, hirsuitism, synophrys, broad nasal bridge, and sparse scalp hair.

Fig 2.—Coarse facial features with microcephaly, hirsuitism, synophrys, broad nasal bridge, and sparse scalp hair.

Fig 3.—Same patient as in Fig 1 at an older age and hair is no longer sparse.

Fig 4.—Same patient as in Fig 1 at an older age and hair is no longer sparse.

Fig 5.—Absence of nail and terminal phalanx of fifth finger.

Fig 6.—Absence of fifth toe nail and hypoplasia of others.

Manifestations

Major manifestations are characteristic facial appearance, mental retardation, and hypoplasia or absence of the nails of the fifth fingers and toes. The facial appearance is coarse with bushy eyebrows, broad nasal bridge, thick lips, broad nose, and synophrys. Mild microcephaly and sparse scalp hair may be present.

The nails of the fifth fingers and toes are frequently absent or hypoplastic and the other toenails may be similarly involved. There may also be an absence of the distal phalanx of the fifth finger or toe, clinodactyly, a small or absent patella, coxa valgus, dislocation of the radial head, and lax joints.

The degree of mental retardation varies but may be quite severe. Feeding problems and frequent respiratory infections occur during the newborn period. Other abnormalities include growth deficiency and hirsuitism.

Roentgenograms demonstrate the aforementioned skeletal abnormalities.

Genetics

At the present time, the mode of inheritance is not definitely known, but thus far occurrences have been sporadic except for a recent report of an affected brother and sister. Chromosomal studies have been normal although there has been one report of a child who resembled the Coffin-Siris syndrome and had partial trisomy of chromosome 9.

Treatment

Although no specific treatment is available, it is important that the patient and family receive supportive care. Special educational programs should be instituted to help the child achieve his or her potential.

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Tuberous Sclerosis

True precocious puberty may be idiopathic in nature or may result from congenital or acquired CNS dysfunction.[1] Tuberous sclerosis has been included among the neurogenic causes of precocious sexual development since Krabbe[2] reported the first two cases with this association in 1922. Since then, several more such patients have been described.[3-8] We describe a patient with tuberous sclerosis who had symptoms of gynecomastia and sexual precocity. The literature is reviewed, and the importance of considering the diagnosis of this dominantly inherited disorder in children with precocious puberty is emphasized.

Report of a Case.—This boy was the product of an uncomplicated 37-week gestation. Psychomotor development was normal. At about age 10 years, the patient was noted to have advanced sexual development and enlarged breasts. His medical history was unremarkable; he had had no seizures and no exposure to exogenous hormones or drugs. The family history showed that the patient's mother began having seizures at age 10 years. On examination, she had an adenoma sebaceum rash over both cheeks, several hypopigmented areas over her body, and periungual fibromas on the toes. She stated that her mother had a similar facial rash.

At age 12 years, the patient was admitted to the Pediatric Neurology Service of Boston City Hospital for investigation of his gynecomastia and early sexual development. His height was 166 cm (greater than the 98th percentile); weight, 53.6 kg (90th percentile); and head circumference, 57 cm (98th percentile). Prominent gynecomastia was present bilaterally; no abdominal masses were palpated. The penis and testes were adult-sized, the latter measuring 4 × 2.5 cm. There was abundant pubic hair in a male distribution (Tanner 5). He had an adenoma sebaceum facial rash, several hypopigmented areas on his back, and left sacral shagreen patch. The results of his neurological examination, including funduscopy, were normal. Wechsler Intelligence Scale for Children testing showed an IQ of 84. Findings from urinalysis, hemogram, and serum electrolyte, blood glucose, renal and liver function tests, and CSF examination were normal. Wrist roentgenograms were consistent with a bone age of 14 years. Skull roentgenogram demonstrated areas of intracerebral calcification that were shown to be periventricular by computerized axial tomography. A pneumoencephalogram with tomography demonstrated a calcified mass projecting into the right lateral ventricle. There was no hydrocephalus, and the third ventricle, basal cisterns, and hypothalamic region were roentgenographically normal.

Endocrine evaluation showed normal serum levels of T4 (7.3 μg/dl; normal, 4 to 11 μg/dl); follicle-stimulating hormone (6.7 ImU/ml; normal adult males, 5 to 25 ImU/ml); luteinizing hormone (15.5 ImU/ml; normal adult males, 5 to 25 ImU/ml); human chorionic gonadotrophin (< 0.32 ng/ml; normal, < 1.0 ng/ml); 17-α-hydroxyprogesterone (516 pg/ml; normal, < 1,000 pg/ml); testosterone (929, 766, and 566 ng/dl; normal adult males, 350 to 1,100 ng/dl); and estradiol (25.5 pg/ml; normal adult males, < 50 pg/ml). Insulin-induced hypoglycemia resulted in a normal response of growth hormone. Adrenocorticotropic hormone stimulation, dexamethasone suppression, and metyrapone test results were all normal. Serum prolactin concentrations (45.6 and 31.6 ng/ml; normal, < 30 ng/ml) were elevated. Chlorpromazine stimulation promoted a doubling of initial prolactin levels.

Comment.—This patient had tuberous sclerosis, sexual precocity, and gynecomastia. The diagnosis of tuberous sclerosis was established by the presence of adenoma sebaceum, hypopigmented skin lesions, shagreen patch, periventricular calcifications, and a family history. Precocious puberty may be established only retrospectively, but even at the time of investigation, the patient's genital development was beyond normal limits for his age.[1] His physical, roentgenographic, and endocrine findings were compatible with true or neurogenic precocious puberty. His breast development was assumed to be adolescent gynecomastia since no other endocrinologic explanation was found.

The patient had an elevated serum prolactin level. An increased serum prolactin level results from disruption of the normal hypothalamic inhibition of prolactin release from the pituitary. Elevation of this hormone level in the serum has been found to be a sensitive indicator of hypothalamic-pituitary dysfunction.[9] Central nervous system processes that have been associated with hyperprolactinemia include craniopharyngioma, chromophobe adenoma, granulomas, histiocytosis X, head trauma, and pituitary stalk section.[10] In our patient, no evidence of a mass lesion was found despite careful investigation. It may be speculated that an unidentified tuberous lesion in the hypothalamic area was the cause of the hyperprolactinemia and of the precocious sexual development.

We were able to find eight patients (four girls and four boys) with precocious puberty and tuberous sclerosis described in the literature.[2-8] The age at which the precocious sexual development first came to medical attention varied from 10 months to 11 years. Endocrine studies consisting of urinary excretion of steroid hormones or bioassayable gonadotrophins were performed on only two patients. These were inadequate by present standards. Clinically, however, the patients appeared to have true precocious puberty.

Only a few cases of tuberous sclerosis and precocious puberty had postmortem examination. In one of Krabbe's patients, a tuber was found

in the region of the mammillary bodies. Several other patients had hydrocephalus, which is occasionally associated with precocious puberty.[1,10]

The diagnosis of tuberous sclerosis is easily made when the classic triad of skin lesions, seizures, and mental retardation is present. It is now known, however, that as many as 30% to 40% of the patients with this disorder may be intellectually normal, and one third of such patients may have no seizures.[11] The skin manifestations may be quite subtle and may be detectable only by careful examination. It is possible, therefore, that in some patients with precocious puberty, the presence of underlying tuberous sclerosis may go undetected. In view of the genetic implications of this dominantly inherited disorder, we suggest that the diagnosis of tuberous sclerosis be considered in children with precocious puberty.

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Nonproprietary Name and Trademarks of Drug

Chlorpromazine—*Thorazine, Chlor-PZ, Chromedazine, Promachel.*

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Hydatid Torsion

Vestigial structures of the embryologic sex duct system may form cysts that produce symptoms requiring surgical intervention. Torsion of these remnants may occur in children or adults of both sexes. Two recent cases of hydatid torsion prompted review of the sites of these remnants and their embryologic origins.

Report of Cases.—CASE 1.—An 11-year-old girl was admitted to the hospital because of right lower quadrant pain and anorexia. For two weeks she had recurrent attacks of pain, starting in the epigastrium, and localizing in the right lower quadrant, without fever, vomiting, change in bowel habits, or dysuria. On examination there was exquisite tenderness in the right lower quadrant with voluntary guarding and no rebound tenderness. On rectal examination there was a tender, walnut-sized mass in the right adnexa. White blood cell count and urinalysis were unremarkable. Surgery was performed with a diagnosis of torsion of an ovarian cyst. A twisted hemorrhagic cyst, 3 cm in diameter, was found arising from the edge of the right fallopian tube at the fimbriated end, a remnant of the caudal tip of the Müllerian duct. Two smaller cysts, 0.3 to 0.6 cm, were also present in the broad ligament, remnants of the mesonephric tubules or cysts of the canal of Gartner. All cysts were excised and an incidental appendectomy performed. Pathologic diagnosis was hydatid remnants. Figure 1 shows the epithelial-lined cyst, with hemorrhage into the cyst wall due to the torsion. Recovery was uneventful and the patient was relieved of attacks of abdominal pain.

CASE 2.—A 2-year-old boy was admitted with sudden onset of pain and swelling of the left scrotum. Examination disclosed a tense, tender mass in the left scrotum with erythema and edema of the scrotal skin. The testis could not be palpated separately from the mass. Torsion of the testes was diagnosed and exploration of the scrotum performed. On opening the tunica vaginalis, a 3-cm gangrenous hydatid with torsion of the pedicle was found cephalad to the normal testis. This hydatid, the paradidymis or the organ of Giraldes, was removed. Postoperative recovery was uneventful.

Comment.—The most common vestigial remnant is the appendix testis,

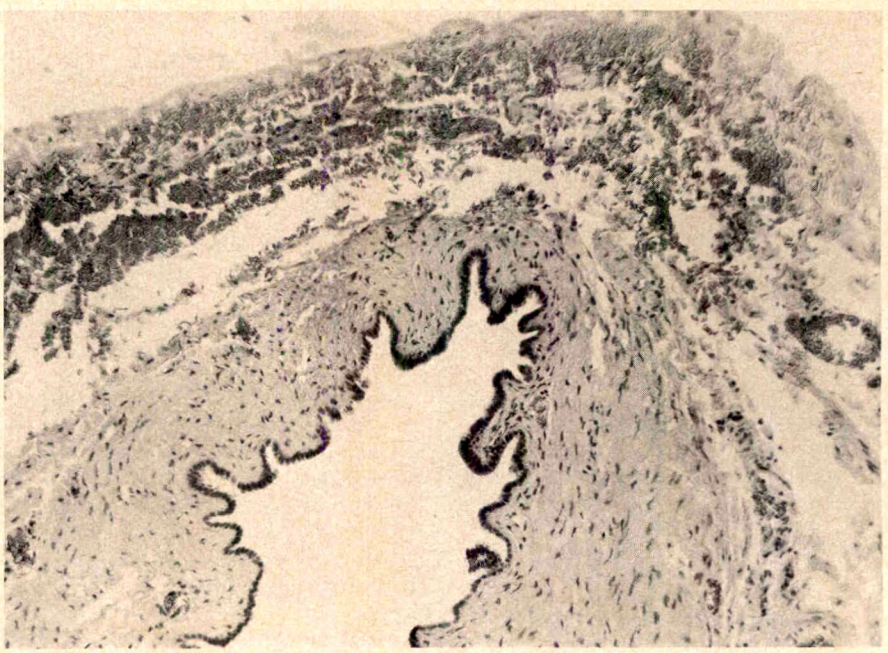


Fig 1.—Hydatid of Morgagni. Cyst lined by low columnar epithelium arranged in single layer. Extensive hemorrhage in wall of cyst (× 160).

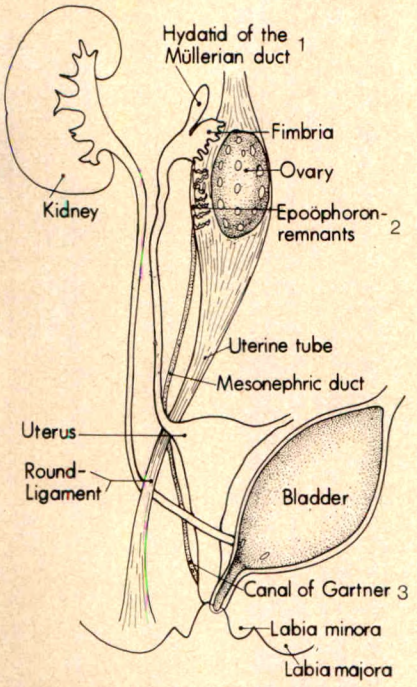
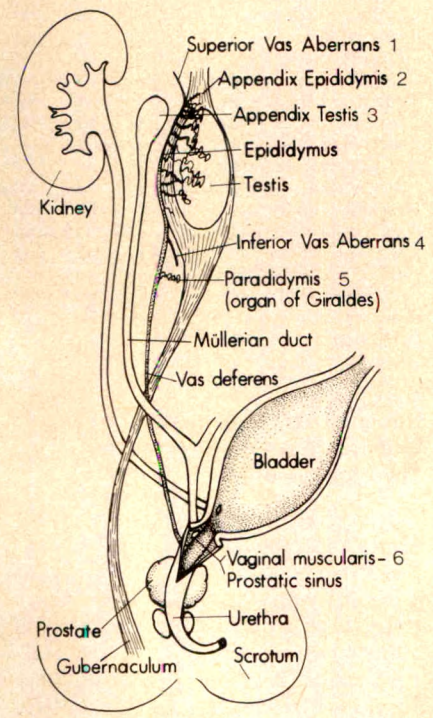


Fig 2.—Developing female reproductive system. Remnants that form cysts are numbered 1, 2, and 3.

Fig 3.— Developing male reproductive system before testicular descent. Remnants may persist at areas numbered 1, 2, 3, 4, 5, and 6.



which was present in 92% of autopsied patients.[1] This remnant, also known as the hydatid of Morgagni, represents the cephalic end of the Müllerian duct. The Müllerian duct may also leave a small diverticulum at its caudal end, the prostatic sinus or vagina masculina. Vestigial mesonephric tubules in the male form the appendix of the epididymis, the penduculated hydatid, which was found in 34% of autopsied cases.[1] The mesonephric tubes also form the paradidymis, or organ of Giraldes, which is usually difficult to identify grossly. Rare additional appendages in the male are the superior and inferior vasa aberrans of Haller (Fig 2).[2]

In the female, the cephalic tip of the Müllerian duct may persist in rudimentary form as a hydatid, attached to the tube or fimbria. Mesonephric tubules and ducts that persist in the female are embedded in the mesovarium and are called *epoophoron*. Less commonly, the distal mesonephric duct may produce remnants in the broad ligament or vaginal wall that are called the canals of Gartner. These remnants may develop cystic enlargements as the small epithelial vesicles accumulate fluid. These cysts can reach considerable size (Fig 3).[2]

Acute torsion of cystic remnants of the primordial sex duct system produce symptoms similar to those of ovarian cyst torsion or testicular torsion and require surgical intervention. When these remnants are seen as incidental findings during operative procedures for other conditions, they should be removed.

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Left Ventricular Myocardial Infarction in Tetralogy of Fallot

Myocardial infarction (MI) is relatively infrequent in infants and children, although its association with anomalous origin of the left coronary artery and other congenital cardiac anomalies that result in coronary hypoperfusion is well known.[1]

Although MI has also been reported in some congenital heart defects without coronary artery abnormalities,[2-4] massive MI of the left ventricle in tetralogy of Fallot (TOF) has not, to our knowledge, been reported.

Report of a Case.—An 8-month-old girl had been followed up elsewhere with the clinical diagnosis of TOF. Although moderately cyanotic, she had no history of hypoxic spells. On the morning of admission, she had an hypoxic spell. Because of poor response to conventional therapy, ie, knee-chest position, sodium bicarbonate, and morphine, she was transferred to our institution. On arrival, she was cool and blue-gray; heart rate was 150 beats per minute; respirations, 80/min; and blood pressure, 60/40 mm Hg. There was a grade 1/6 short, ejection systolic murmur at the mid-left sternal border. Morphine, oxygen, sodium bicarbonate, and methoxamine were administered intravenously. Blood analysis while breathing 100% oxygen showed a pH of 7.27 and Po_2 of 35 mm Hg. Hematocrit value was 42%; hemoglobin, 13.0 g/dl; RBCs, 6.5 million/cu mm; and WBCs, 21,500/cu mm.

An ECG just prior to admission had demonstrated right ventricular hypertrophy with an anterior T vector. The ECG on admission was drastically changed and suggested acute posterolateral MI (Fig 1).

Although the patient's clinical condition improved, the ECG remained unchanged and bouts of ventricular tachycardia subsequently developed that responded to intravenously given lidocaine. She was taken to the operating room on the following morning for a Blalock-Taussig anastomosis. A cardiorespiratory arrest occurred at the induction of anesthesia. The chest was opened quickly, and the heart massaged effectively. The patient was placed on cardiopulmonary bypass in order to perform total correction, but after complete repair was accomplished, cardiac function deteriorated, and she died in the operating room.

Autopsy showed TOF with a technically satisfactory surgical repair. Both coronary arteries were normal in origin and distribution. Although there were interstitial hemorrhage and edema associated with surgical trauma, distinct from these areas was a recent transmural myocardial infarction measuring 2.6 × 1.8 cm and involving the posterolateral wall of the left ventricle. The early invasion by polymorphonuclear leukocytes placed the age of infarct at greater than six hours (Fig 2). Although a recent thrombus was located in the left anterior descending coronary artery, it did not correspond with the distribution of the major extent of the infarct and was believed to be a late event.

Comment.—Tetralogy of Fallot is a form of cyanotic congenital heart

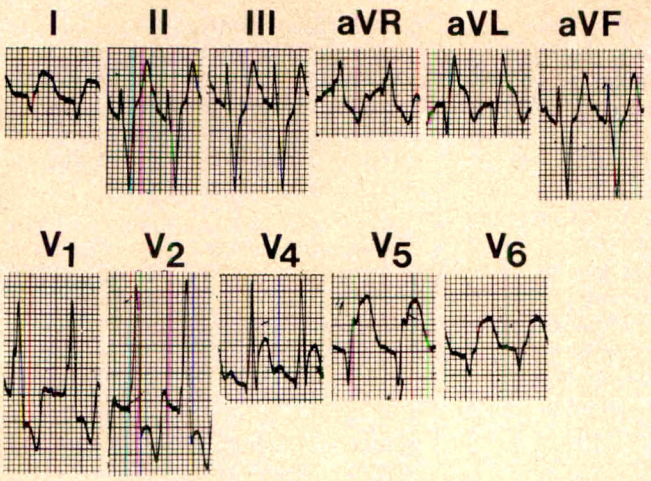


Fig 1.—Electrocardiogram demonstrates acute lateral myocardial infarction. ST-T changes in leads V_1 and V_2 also suggest true posterior wall infarction.

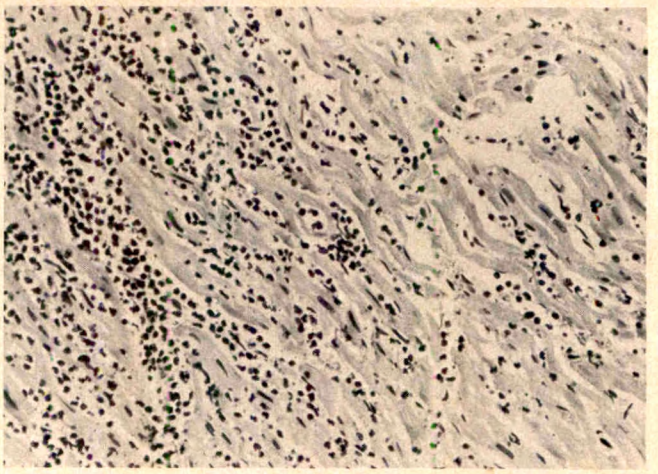


Fig 2.—Very recent myocardial infarction with loss of fibrillar structure and disappearance of nuclei in myocardial fibers. Presence of polymorphonuclear leukocytes is indication of recent process, at least six hours old (×160).

disease with a large ventricular septal defect (VSD) and right ventricular outflow (RVO) obstruction. Although cyanosis may be apparent in the neonatal period, the degree and age at onset depends on the severity of RVO obstruction. Hypoxic spells are associated with RVO spasm with a marked reduction of an already compromised pulmonary blood flow and an increase in right-to-left shunt through the VSD that results in marked hypoxemia.[5,6]

Myocardial infarction has also been reported in a variety of congenital heart diseases other than those with obvious coronary artery abnormalities. Franciosi and Blanc,[2] in a necropsy study, stressed the prevalence of MI in pulmonary valvular stenosis (89%), total anomalous pulmonary venous return (80%), aortic stenosis (100%), and transposition of great vessels (38%). Esterly and Oppenheimer[3] reported 62 cases of TOF, eight of which (12%) had MI. However, these infarcts were diffuse and microscopic, presenting no clinical problem, and were exclusively limited to the subendocardium and papillary muscle of the hypertrophied ventricle. This preferential localization of the infarcts to one ventricle was attributed to relative coronary insufficiency secondary to increased myocardial mass. In contrast to the reports mentioned previously, the infarct in our patient was large enough to be clinically diagnosed and occurred in the left and not the right (obstructed and hypertrophied) ventricle.

Myocardial infarction has also been reported in children with lymphoma,[7] coxsackievirus infection,[8] mucocutaneous lymph node syndrome,[9,10] and in the newborn due to cardiogenic shock.[11] Cerebral infarcts in hypoxic spells due to thrombotic episodes and or anoxia are rather common.[12] Although the importance of iron deficiency anemia has been stressed, its role in myocardial infarction has not been evaluated.

Left ventricular MI should be added to the list of complications of hypoxic infants with TOF. Although the condition has not, to our knowledge, been previously reported, it may occur more frequently and can be considered a lethal complication.

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Neonatal Thyrotoxicosis in Four Siblings Born to a Previously Thyrotoxic Mother

Neonatal hyperthyroidism is a relatively uncommon disorder. It has been described in infants born to women with active hyperthyroidism and in those born to euthyroid women previously treated medically or surgically for hyperthyroidism.[1] Recent evidence suggests that neonatal hyperthyroid-

ism is due to thyroid stimulation in the fetus by a transplacentally acquired long-acting thyroid stimulation globulin (LATS) or a human specific antibody, LATS-protector (LATS-P), which has been detected in a large number of patients with hyperthyroidism.[2] Although there have been reports of neonatal thyrotoxicosis, this report is the first to our knowledge to describe its consecutive occurrence in four siblings born to a previously thyrotoxic woman.

Report of Cases.—The mother is a 40-year-old, gravida 6, para 4, abortus 2 woman who was well until 1950 when, at the age of 16, hyperthyroidism developed and she underwent a partial thyroidectomy and a course of iodine 131 therapy. She then became euthyroid and asymptomatic, and took no medication for a period of 18 years. During this time she was delivered of three premature infants, all of whom had thyromegaly and a syndrome consistent with neonatal thyrotoxicosis (Table). Although a definitive diagnosis is not possible, neonatal thyrotoxicosis is suggested in cases 1 and 3 on the basis of clinical presentation, elevated serum protein-bound iodine (PBI) level, and response to therapy. In addition, patient 3 had an advanced bone age. Similarly, a presumptive diagnosis can be made in case 2 on the basis of the clinical finding of thyromegaly and the autopsy finding of thyroid hyperplasia.

In 1968, the mother started to require thyroid replacement. Thyroid studies in 1972 showed the following values: serum triiodothyronine, 27.8 μg/dl (normal, 23 to 35); serum thyroxine (T_4), 1.8 μg/dl (normal, 2.7 to 7.4); and PBI, 2.0 μg/dl (normal, 4 to 8). During this period, she had two pregnancies; one terminated as a spontaneous abortion and the other as a stillbirth at 32 weeks' gestation.

Our patient was the fourth infant born alive in the sibship. She was born in 1974 when the mother was well controlled and in a euthyroid state with a regimen that consisted of levothyroxine sodium (Synthroid), 0.1 mg daily, propranolol hydrochloride (Inderal), 10 mg thrice daily, and hydrochlorothiazide (Hydrodiuril), 50 mg every other day. The signs and symptoms and serum T_4 levels as well as the response to treatment with Lugol's solution in this child are compatible with the diagnosis of neonatal thyrotoxicosis (Table). Thyroid-stimulating immunoglobulin (TSI) level assayed in the mother's serum was found to be significantly elevated.

Comment.—Previous reports have shown that the sera of patients with Graves' disease contain at least two types of TSIs—LATS and LATS-P.[2] Both of these antibodies are 7S γ_2-globulins produced by the circulating maternal lymphocytes and are capable of placental transfer to the fetus.[3,4] Cases of neonatal thyrotoxicosis have been reported in which (1) LATS was present in both the mother and the infant; (2) LATS was present in the mother but not the infant; (3) LATS was present in neither the mother nor the infant, but LATS-P was detected in the mother; and (4) LATS was present in neither and LATS-P was detected in both the mother and infant.[5] Neither our patient nor her mother had LATS present in the sera; however, the mother had significant elevation of serum TSI level. Since serum TSI level is a measurement of LATS and LATS-P together, an elevated serum TSI level with a negative LATS level indicates the presence of LATS-P in the maternal serum. Unfortunately, not enough serum was obtained from the infant to measure her TSI level during the first few days of life.

The occurrence of the clinical and/or chemical syndrome of neonatal thyrotoxicosis in a succession of infants born throughout a period of 18 years to a previously thyrotoxic woman indicates that thyroid-stimulating antibody may persist in patients for a prolonged period of time. In light of this, it is interesting to note that thyrotoxicosis in successive infants has not been reported previously, to our knowledge. This may indicate that variations in host response

Clinical History of Infants Born to a Previously Thyrotoxic Woman

Year	Gestational Age, wk	Sex	Weight, g	Signs and Symptoms*	Laboratory Findings	Treatment	Remarks
1956	34	M	2,240	AGA, irritability, hyperactivity, tachycardia, diarrhea, cardiomegaly, thyromegaly	Infant: PBI (5th day), 14.0 mg/dl (normal, 9.1-12.7)	Digoxin	Symptoms resolved in 5 wk; alive and well
1961	32	M	900	SGA, congestive heart failure, hepatosplenomegaly, thyromegaly	No thyroid studies done	Treated for congestive heart failure	Died at 3 days; postmortem: thyroid hyperplasia, meningitis, pneumonitis, myocarditis, hepatitis
1963	32	F	1,420	AGA, irritability, diarrhea, hyperactivity, high pitched cry, tachycardia, murmur, exophthalmus, thyromegaly	Infant: PBI (1st day), 11.7 μg/dl (normal, 8.7-11.5); I^{131} uptake elevated; bone age, 6 mo advanced Mother: PBI, 8 μg/dl (normal for nonpregnant, nonestrogen-treated woman, 4-8)	Lugol's iodine	Symptoms resolved in 5 wk; alive and well
1974	39	F	2,300	Tachycardia in utero; emergency cesarean section for fetal distress; SGA, meconium stained, fever, hyperactive, irritable, diarrhea, petechiae and ecchymoses (thrombocytopenia), tachycardia, hepatosplenomegaly, thyromegaly	Infant: T_4 (cord), 21.2 μg/dl (normal, 7.3-15.3); T_4 (3rd day), 29.8 μg/dl (normal, 9.8-16.6); LATS, none detected; TSI†, insufficient sample Mother: LATS, ±; TSI, 65%, 78%, 77% (≤90% is significant level)	Lugol's iodine	Symptoms resolved in 12 wk; alive and well

*AGA indicates appropriate for gestational age; SGA, small for gestational age.
†Thyroid-stimulating immunoglobulins, including both LATS and LATS-P.

or in genetic susceptibility may modify the expression of the disease in the newborn.[6,7]

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Joseph P. Kriss, MD, Stanford University Hospital, helped in the TSI assay.

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Hyperchloremic Metabolic Acidosis With Cholestyramine Therapy for Biliary Cholestasis

Cholestyramine is a hydrophilic, insoluble anion-exchange resin that removes substantial amounts of bile acids from the enterohepatic circulation by binding them in a compound that cannot be reabsorbed through the intestine. It has been used without complication in children with biliary cholestasis associated with biliary atresia[1] and in the treatment of intractable diarrhea in infants.[2,3] The case reported here deals with hyperchloremic acidosis as a complication of cholestyramine therapy in a 6-month-old infant with intercurrent infection, and adds to other reports of this finding by Hartline,[4] Primak and McGurk,[5] and Kleinman.[6]

Report of a Case.—The patient was first referred to the pediatric consultation service at Mt Zion Hospital in San Francisco at the age of 10 weeks, when a diagnosis of intrahepatic cholestasis secondary to intrahepatic biliary atresia was made and confirmed by open liver biopsy. Cholestyramine therapy was begun six weeks prior to this admission, without adverse reaction. He was followed up in his home community by his local pediatrician, returning bimonthly to our service for continued evaluation. At the age of 6 months, he was readmitted with a chief complaint of ear infection and increased bleeding tendency, after an illness of six days. His parents reported decreased appetite. On admission, he was irritable and lethargic; there was no history of diarrhea, and he appeared to be well hydrated. Physical examination disclosed a questionable left otitis media, bleeding from both ears, and continued bleeding from venipuncture and injection sites. He was extremely tachypneic, and the liver edge wes sharp, firm, and palpable 2 to 3 cm below the right costal margin. Medications at the time of admission were ampicillin, vitamin D, vitamin E, a vitamin mixture (Poly-Vi-Sol), phenobarbital, and cholestyramine, 16 mg daily. All medications were stopped, and cultures of blood, urine, CSF, and stool were taken. (These were all negative after 72 hours.)

Chest roentgenogram and ECG were normal. Laboratory values were as follows: serum cholesterol, 1,100 mg/dl; total bilirubin, 10.2 mg/dl (direct reaction, 8.0 mg/dl); alkaline phosphatase, 1,720 mU/ml (normal for age, 300 mU/ml); SGOT, 305 mU/ml (normal, < 40 mU/ml); prothrombin time, 35.9 seconds (normal, < 11.9 seconds); partial thromboplastin time, 99.9 seconds (normal, < 40 seconds); fibrinogen, 320 mg/dl (normal, < 170 mg/dl); hematocrit, 28.2%; hemoglobin, 9.6 g/dl; WBCs, 14,800/cu mm, with normal differential; BUN, 26 mg/dl; creatinine, 0.8 mg/dl (normal, < 1.5 mg/dl). Capillary blood gas analysis disclosed the following values: pH of 6.88; Po_2, 66 mm Hg; Pco_2, 23 mm Hg. Serum sodium level was 132 mEq/liter; chloride, 112 mEq/liter.

Treatment of the hyperchloremic acidosis was begun with intravenous infusion of 27 mEq of sodium bicarbonate over the next hour and final replacement with orally given sodium citrate. Serum potassium concentration decreased to 2.8 mEq/liter, with correction of the acidosis, and the deficit was replaced intravenously. Electrocardiographic findings remained normal. The increased prothrombin and partial thromboplastin times were corrected with intramuscular injection of phytonadione (Aquamephyton).

The acidosis resolved within 12 hours; the infant was alert, active, and happy at discharge four days later. Discharge medications included vitamin E, vitamin D, phytonadione, 5 mg orally once a week, phenobarbital, and a commercially prepared formula (Pregestimil). He has continued to be well since discharge.

Comment.—The use of cholestyramine without complication in the treatment of diarrheal illness in infants has been reported by Blanckaert and Farriaux[2] and Wagner et al.[3] In a case reported by Kleinman,[6] cholestyramine was tolerated by a child with biliary atresia until she was 10 years of age, when reduced creatinine and inulin clearance developed. However, the occurrence of hypernatremia and hyperchloremic acidosis in two patients with intercurrent illness has recently been reported by Primak and McGurk,[5] and Hartline[4] has reported hyperchloremia in infants treated with cholestyramine during diarrheal illness. In our patient, cholestyramine was tolerated for a period of six weeks without complication until the onset of an upper respiratory infection and otitis media. In this case, correction of the hyperchloremic acidosis and restoration of normal electrolyte balance were accomplished by intravenous therapy. The precipitating infection resolved with antibiotic therapy.

Since chloride ion is excreted principally by the kidney,[7] any clinical situation that reduces renal blood flow or renal function can result in chloride ion retention and acidosis. When an intercurrent febrile or diarrheal illness develops in a child or infant who is receiving cholestyramine therapy, it should probably be discontinued until adequate fluid intake and urine output are certain. Frequent electrolyte determinations are necessary in a child or infant receiving cholestyramine, especially during an intercurrent illness.

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Books

Foster Care in Five States: A Synthesis and Analysis of Studies From Arizona, California, Iowa, Massachusetts, and Vermont, DHEW Publication No. (OHD) 76-30097, by Shirley M. Vasaly, 150 pp, 50 illus, Department of Health, Education, and Welfare, 1976.

Foster Care in Five States is an important, stimulating, and provocative review of studies from Arizona, California, Iowa, Massachusetts, and Vermont. Anyone concerned with optimal foster care or concerned with planning for the needs of dependent children should read this report. The seven major topics; foster care system, natural families, foster children, agency staffing and services, fiscal consideration, community involvement, and conclusion, are well outlined with excellent summary recommendations for improved services and for community involvement. Community pediatricians who are concerned with the general needs of children, child abuse problems, and foster care in the community can quickly become acquainted with the general needs and deficiencies of our current system of providing care for children. This report will identify and clarify the role of the community in participation in these needed problems.

The inequities of local funding as well as the small pool of adequately trained social workers are clearly seen to be major difficulties in identifying and treating family problems.

Among the states studied, the need for placing a child in the foster care program variously included abuse, abandonment, parents' absence (including divorce, separation, imprisonment), parents' physical illness, mental illness or death, adoption planning, or the child's behavior or disability. Child abuse or neglect, as a reason for placement, varied from one state to another from 14% to 51%. Furthermore, the services available to families before placement of the child seemed to be very meager, possibly because of understaffed social service facilities. In some states, no services could be available to a child unless the child is in foster care, thus encouraging unnecessary placements. A representative survey of natural parents in Massachusetts showed that 66% of the natural parents interviewed believed that placements would have been avoidable if the crisis had been helped by in-home services, day-care, or financial assistance. Furthermore, 60% of these parents felt excluded from the participation in planning for their child.

Foster parents are team members in the foster care system because the day-to-day responsibility for the welfare of the children is in their hands. This is especially true under existing conditions of overburdened and inadequately trained workers. As a vital part of agency staffing, these foster parents require support services, adequate facilities for the children's needs, training for their role, information on the children to be placed with them, adequate reimbursement of costs incurred and recognition of their contribution to the program. Continuity of the foster family placement is essential to the emotional adjustment of the child. In a review of the foster parents' attributes, it is found that most of them are high school graduates. They have an average of about three or four children per home and they are very stable, having been at their same address for more than ten years. Most of them have reported that they became interested in foster care through a friend or relative and 96% said that they were aware of the need for foster homes and wanted to help children. Only 3.4% were motivated by financial reasons. Cost of rearing these children is much greater than the low remuneration they receive. There is usually no provision for the care of the children while the foster parents are on vacation; there is confusion over agency policy on what constitutes "special needs."

The statement on p 60 of this report that medical treatment was denied on occasion due to refusal of medical services to accept medicaid payment is of great concern to all pediatricians who are an important link in advocacy for the children involved in family disruption.

As a community leader, the pediatrician can point the way to improved techniques for dealing with the problems of foster care. It is clear that we need better education for parenting, adequate use of volunteer sources in the community for supplementing and complementing our overworked and underbudgeted social service facilities, facilities for crisis intervention, and concern for the foster parents' needs and their education in meeting the needs of the children in their care.

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The Genetic Approach to Human Disease, by Vincent M. Riccardi, 273 pp, 38 illus, $13.95 ($7.95 paper), Oxford University Press, 1977.

According to the author, this book is designed to show what the clinical application of genetic principles can accomplish. In the introductory chapters, the reader is introduced to the contemporary working classification of medical genetics: chromosomal disorders, disorders with Mendelian patterns of inheritance, and polygenic disorders. There is an abbreviated chapter on biochemical errors of inheritance. This is followed by chapters on environmental influences on the fetus, genetic evaluation, prenatal diagnosis, genetic evaluation and counseling, roles of ancillary personnel in clinical genetics, therapy of genetic disorders, pharmacogenetics, ethical, moral, and legal aspects, and finally a description of a regional genetic counseling program.

The chapters on pharmacogenetics,

biochemical disorders, and ethical, moral, and legal aspects are very short, and hardly can present an adequate picture of this complicated subject. The final chapter describing a regional genetic counseling program seems not adequately relevant in this textbook. In fairness to the author, it should be stated that there is no evidence that the book was intended to be encyclopedic with respect to human genetics. There are other books that serve such a purpose.

As an introduction to the state of the art of contemporary applied medical genetics, the volume is quite adequate in spite of the shortcomings noted previously. The paperbound edition is relatively modest in cost. It is up to date, and gives a realistic presentation of what is available to the patient in clinical genetic units around the country. It is highly recommended as a textbook for courses in medical genetics given to medical and nursing students and to other professionals who may be involved in the applications of genetic knowledge to patient care.

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Allergic Disorders in Children, edited by M. Studenikin and T. Sokolova, $6.75, 446 pp, Moscow, Mir Publishers, 1977.

Two principal facts make this Soviet publication on "Allergic Disorders in Children" especially rewarding to review: the information it contains is up to date, concise, lucidly presented, and totally relevant, practically as well as theoretically and it provides the Western reader with a detailed view of this important aspect of Soviet clinical science and demonstrates the desire of the authors and of the publishers to share this information with English-speaking physicians across the Atlantic.

In the relatively short space of 446 pages, the prominent specialists from Moscow, under the editorship of academicians Professor M. Studenikin and Professora T. Sokolova (the American reader will be impressed by the major contributions of women to this work), have succeeded in presenting an abundance of pertinent data. All those interested in the practice of pediatric allergy will derive from these pages sufficient knowledge to improve their diagnostic skills, to expand their understanding of the pathophysiology of immunologic disorders in children, and to enhance their ability of treating these rationally and effectively. Basic immunologic concepts and techniques, standard diagnostic procedures (including the establishment and the operation of an allergy diagnostic laboratory, the administration of bronchial inhalational challenges, etc) and various therapeutic approaches are discussed in sufficient detail, but without excessive verbosity. Particularly useful for physicians and patients traveling to the USSR will be the recognition of new terms for old familiar drugs, such as Novodrin for isoproterenol sulfate, Euphyllin for aminophylline, Dimedrol for diphenhydramine hydrochloride (Benadryl) etc, as well as learning about exclusive Soviet preparations, such as the antihistamines Diazolin and Phencarol. For the pediatrician concerned with genetic counseling, important statistics and guidelines on clinical genetics are presented, perhaps with somewhat greater emphasis on positive familial incidence and with less discussion of the equally interesting negative or discordant data. Consideration of the molecular genetics of allergy is relatively brief and seems inadequate, but, admittedly, no definitive data are yet available on this subject. Among other statistical figures of exceptional interest, is the report of a 70%-incidence of specific antibodies to food and microbial antigens (type not specified) among patients with allergy, compared to a 20%- to 30%-positive incidence, in generally lower titers, among nonallergic individuals.

The question of a relative adrenal insufficiency in relation to the pathogenesis of allergic disease is considered in much detail, referring back to the original work of Selye, which has been somewhat neglected in the West. The possibility of altered cortisol kinetics in patients with allergy is also mentioned with some data to support it, but with little reference to contradictory findings. Some areas of possible stronger disagreement, which must be recognized to be fruitfully debated and to permit an eventual consensus of opinion, include the use of cardiac stimulants for severe episodes of asthma and anaphylaxis, the total dosage of hyposensitization injections, and the use of bacterial vaccines for diagnostic skin tests and for the immunotherapy of allergic disorders. The nearly seven pages devoted to histaglobin therapy of respiratory allergy, may raise more questions than they provide answers, in view of the fact that this form of therapy has not gained acceptance in the United States. Such often debated problems as the incidence and prevention of deaths from asthma, the role of respiratory infection in allergy, environmental, and dietary aspects, etc, are treated with a remarkably open mind and with due consideration to the current varying points of view. Serous otitis media is the only presumably allergic condition, not considered in sufficient detail, perhaps because it is not as common in the USSR, as it is in North America. Various nonatopic forms of allergy are described in sufficient and instructive detail.

The bibliography is quite adequate and contains a well-balanced proportion of Soviet and Western references. The inclusion of individual case reports in this book should be particularly illuminating for the practicing clinician and, with the characteristic Russian names of the patients, such as Andrei, Igor, Natasha, etc, it adds a welcome attraction to this English version of the original Russian text.

The English translation is not simply adequate, but impressively good, indicative of the translator's (Dr L. Askenova) thorough familiarity with the nuances of scientific English. The only point where a question might be raised, is the rendering of the proposed new terms chimergic and kitergic in Professor Ado's classification of allergic reactions (p 10). A more appropriate Greek-to-Russian-to-English transliteration might have been chymergic and cytergic, respectively.

This reviewer feels an obligation to express his sincere thanks—bol'shoe spasibo—for the opportunity of reviewing this outstanding current contribution to the pediatric allergy literature. Let us hope that North American pediatricians, allergists, and all medical book publishers will reciprocate by sending their current and future books to the USSR for review.

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What they drink at the stork club.

Four generations ago, we founded our exclusive Stork Club. And ever since, we've been serving members nothing but the best—Carnation Evaporated Milk.

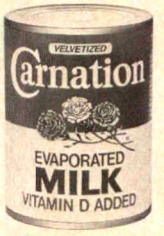
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A new indication for Septra

Getting a child with an earache off to sleep is hard enough, without getting her up again. With the q.i.d. and t.i.d. dosages of other antibacterials for acute otitis media, expecting compliance may be expecting a lot. Septra b.i.d. dosage convenience can change all that.

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Septra Suspension has proved highly effective in acute otitis media caused by the most common middle ear pathogens—*Haemophilus influenzae* and *Streptococcus pneumoniae.*

Though crystalluria has not been a problem with Septra, adequate fluid intake should be maintained and frequent urinalyses with careful microscopic examination performed during therapy. Septra is contraindicated in infants under two months. **Septra should not be used in the treatment of streptococcal pharyngitis.**

†Data on file, Medical Department, Burroughs Wellcome Co.
See last page of this advertisement for prescribing information.



"middle-of-the-night" dose acute otitis media*

Septra®

Suspension

Each teaspoonful (5 ml) contains:
40 mg trimethoprim and 200 mg sulfamethoxazole

b.i.d.

through-the-night efficacy against major middle ear pathogens

*Septra is now indicated for use in acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in the judgment of the physician Septra offers some advantage over the use of other antimicrobial agents. Limited clinical information is presently available on the effectiveness of treatment of otitis media with Septra when the infection is due to *Haemophilus influenzae* resistant to ampicillin. To date, there are limited data on the safety of repeated use of Septra in children under two years of age. Septra is not indicated for prophylactic or prolonged administration in otitis media at any age.



Septra® introduces b.i.d. dosage convenience to the treatment of acute otitis media in children

Septra® Suspension

Each teaspoonful (5 ml) contains:
40 mg trimethoprim and 200 mg sulfamethoxazole

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- well tolerated by infants and children† (Contraindicated in infants under two months. See brief summary below for possible adverse reactions.)

Septra® Tablets

Each tablet contains:
80 mg trimethoprim and 400 mg sulfamethoxazole

- available in pleasant tasting cherry-flavored suspension or in tablet form for use in older children
- encourages compliance; unlike other antibacterials for otitis media, Septra requires no middle-of-the-night dose

---

Septra® Tablets and Suspension

Indications and Usage:

ACUTE OTITIS MEDIA: **For the treatment of acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in the judgment of the physician Septra offers some advantage over the use of other antimicrobial agents. Limited clinical information is presently available on the effectiveness of treatment of otitis media with Septra when the infection is due to *Haemophilus influenzae* resistant to ampicillin. To date, there are limited data on the safety of repeated use of Septra in children under two years of age. Septra is not indicated for prophylactic or prolonged administration in otitis media at any age.**

Contraindications: Hypersensitivity to trimethoprim or sulfonamides. Pregnancy and during the nursing period. Infants less than two months of age.

Warnings: SEPTRA SHOULD NOT BE USED IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS.

Clinical studies have documented that patients with Group A β-hemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with Septra than do those patients treated with penicillin as evidenced by failure to eradicate this organism from the tonsillopharyngeal area.

Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias. Experience with trimethoprim alone is much more limited, but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides.

Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBCs are recommended: therapy should be discontinued if a significant reduction in the count of any formed blood element is noted.

Precautions: Use with caution in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur (frequently dose-related). During therapy, maintain adequate fluid intake and perform frequent urinalyses with careful microscopic examination and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Septra. *Blood Dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic Reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal Reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *C.N.S. Reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous Reactions:* Drug fever, chills, and toxic nephrosis with oliguria and anuria. Periarteritis nodosa and L.E. phenomenon have occurred. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia; cross-sensitivity may exist with these agents. In rats, long-term administration of sulfonamides has produced thyroid malignancies.

Dosage and Administration: Not recommended for use in infants less than two months of age.

ACUTE OTITIS MEDIA IN CHILDREN: The recommended dose for children with acute otitis media is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, given in two divided doses every 12 hours for 10 days. The following table is a guideline for the attainment of this dosage using Septra Tablets or Suspension.

Children: Two months of age or older:

Weight		Dose—every 12 hours	
lb	kg	Teaspoonfuls	Tablets
20	9	1 (5 ml)	½
40	18	2 (10 ml)	1
60	27	3 (15 ml)	1½
80	36	4 (20 ml)	2 (or 1 DS tablet)

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual Standard Regimen
15–30	Half of the usual dosage regimen
Below 15	Use Not Recommended

Supplied: SEPTRA TABLETS containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 40, 100, 500 and 1000 tablets; unit dose pack of 100. ORAL SUSPENSION, containing the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole in each teaspoonful (5 ml), cherry flavored—bottle of 450 ml.

Also available in double strength, oval-shaped, pink, scored tablets containing 160 mg trimethoprim and 800 mg sulfamethoxazole—bottles of 60 and unit dose packs of 100.

*Clinical results do not necessarily correspond with *in vitro* data.

†Data on file, Medical Department, Burroughs Wellcome Co.

Wellcome

Burroughs Wellcome Co.
Research Triangle Park
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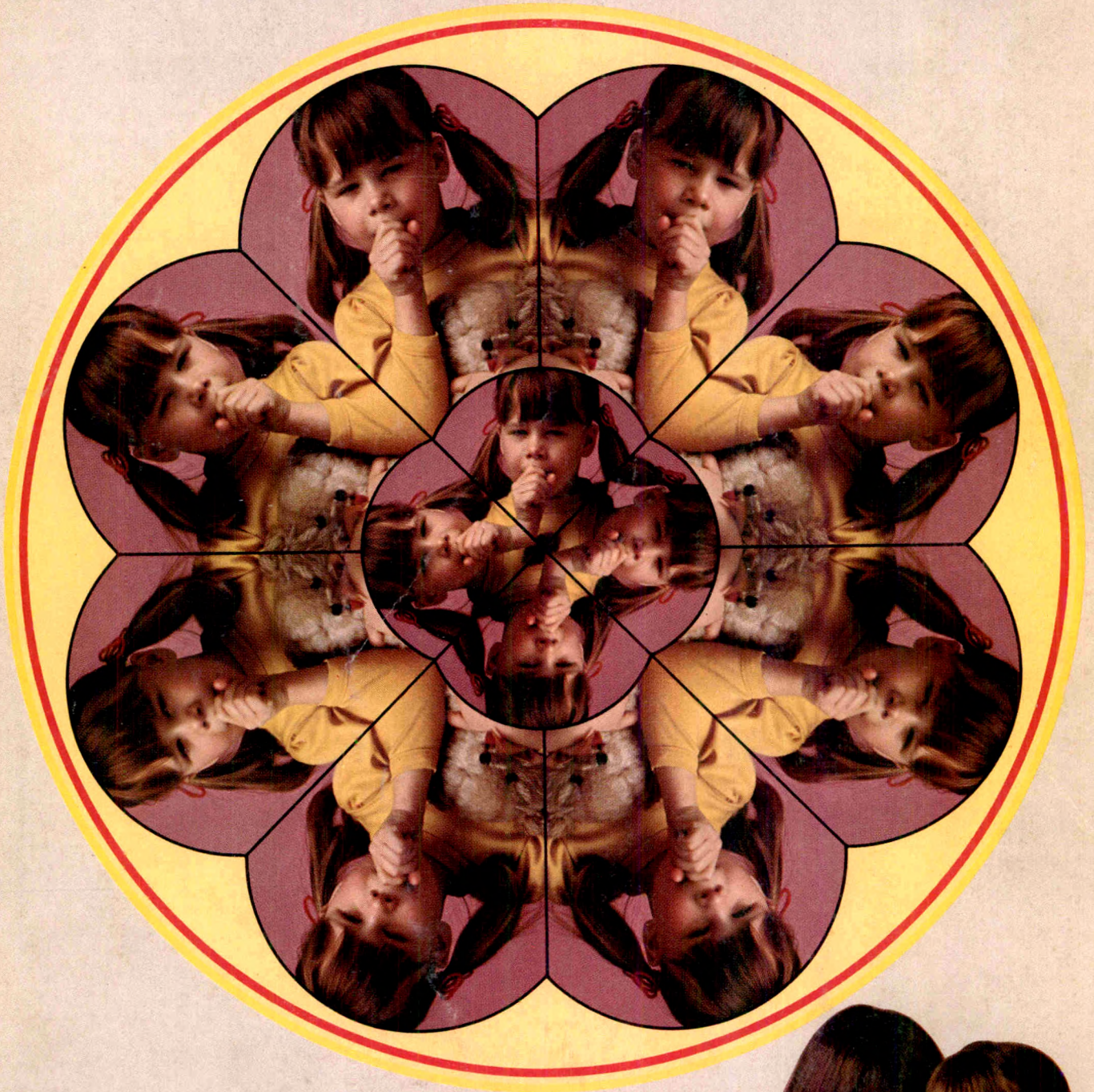
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